Management of Acquired Thrombophilic Disorders in 2011: Focus on Heparin-induced Thrombocytopenia, Antiphospholipid Syndrome, Myeloproliferative Neoplasms and Paroxysmal Nocturnal Hemoglobinuria

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Abstract
Arterial and venous thrombosis are interrelated disorders at the interplay of platelets and fibrin. Arterial thrombi are platelet-rich and occur at sites vulnerable to atherosclerotic plaque rupture where blood shear rates are high; on the contrary, venous thrombi occur in association with slow blood flow and shear rates. These differences may underlie why anti-platelet agents are more effective in prevention of arterial thrombosis, while anticoagulants are preferred for venous thrombosis. Although some common thrombophilic disorders (e.g., Factor V Leiden, prothrombin gene mutation, etc.) are almost exclusively associated with venous thromboembolism, there are several disorders that are important to consider when caring for patients with both arterial and venous thromboembolism. This article will review the evidence-based management of heparin induced thrombocytopenia with thrombosis, anti-phospholipid antibody syndrome and catastrophic anti-phospholipid antibody syndrome, thrombohemorrhagic manifestations of Philadelphia chromosome-negative chronic myeloproliferative neoplasms including polycythemia vera, essential thrombocytopenia and primary myelofibrosis, as well as paroxysmal nocturnal hemoglobinuria.

Arterial Thromboses
Relationship between arterial and venous thrombosis

Although historically and anatomically, arterial and venous thrombosis have been classified into two different categories, there is a growing body of evidence that they share some risk factors and influence the incidence of each other. In a large epidemiologic study from Denmark, investigators retrospectively compared the risks of myocardial infarction (MI) and stroke in more than 25,000 patients with deep vein thrombosis (DVT), approximately 17000 patients with pulmonary embolism (PE) and 163000 controls, using nationwide Danish medical databases. Patients with baseline hypertension, coronary artery disease, stroke or transient cerebral ischemic attack were excluded. Compared to population controls, patients with venous thromboembolism (VTE) (DVT and PE) had a substantially increased risk of MI and stroke during the first year after their VTE. Patients with DVT had a relative risk for MI of 1.60 [95% CI, 1.35 – 1.91] and for stroke of 2.19 (1.85 – 2.60). Patients with PE had a relative risk for MI of 2.60 (2.14 – 3.14) and for stroke of 2.93 (2.34 – 3.66). Relative risks of MI and stroke remained elevated, but less markedly (1.2 – 1.4), during the subsequent 20 years of follow-up.

Biology and risk factors
While arterial and venous thromboemboli both are composed of platelets and fibrin, arterial thrombosis (platelet-rich white clots) have a propensity to occur at sites of arterial plaque rupture where blood shear rates are high; in contrast, venous thrombi (red cell-rich red clot) tend to occur at sites where the venous wall is often normal, but blood flow and shear rates are low. These differences explain in part why anti-platelet agents are more effective for arterial thromboprophylaxis and anticoagulants are superior for prevention of venous thromboembolism. Major risk factors for arterial thrombosis include tobacco smoking, high blood pressure and hyperlipidemia, whereas major risk factors for venous thrombosis are trauma, surgery, and cancer. Nevertheless, on a molecular scale, venous and arterial thrombosis share many risk factors. Activation of inflammation and the hemostatic system after tissue injury, contributes to the pathogenesis of both atherogenesis as well as thrombogenesis. Furthermore, risk factors for arterial thromboembolism also contribute to venous thrombotic risk including age, immobility, obesity, smoking,2,3 the metabolic syndrome,4 renal failure,5 microalbuminuria,6 low high-density lipoprotein (HDL)-cholesterol,7 hyperhomocysteinemia,8 and estrogen. Underscoring the connection between atherogenic risk factors and VTE are based on results reported from the Jupiter study which randomized patients to rosuvastatin or placebo. These investigators found that rosuvastatin reduced the incidence of VTE by 43% in apparently healthy subjects with normal low-density lipoprotein (LDL)-cholesterol and an elevated high-sensitivity C-reactive protein during a median follow up of 1.9 years.8

While most thrombophilic states such as factor V Leiden primarily increase the risk for VTE (excluding a paradoxical embolism due to a patent foramen ovale), several exceptions to this rule exist which are important conditions for the practicing clinician to consider when faced with a patient with both arterial and venous thromboembolism. These entities include heparin-induced thrombocytopenia (HIT), antiphospholipid antibody syndrome (APS), myeloproliferative neoplasms (MPN), paroxysmal nocturnal he-
moglobinuria (PNH), and Trousseau’s syndrome. Since there are many reviews focusing on Trousseau’s syndrome, we will focus on the management of other common causes of venous and arterial thromboembolism; HIT, APS, catastrophic APS, thrombo-hemorrhagic manifestations of MPNs, and PNH.

**Heparin induced thrombocytopenia/thrombosis (HIT/T)**

Heparin-induced thrombocytopenia with thrombosis (HIT/T) is an immune-mediated pro-thrombotic disorder caused by heparin-dependent, platelet-activating IgG antibodies that recognize complexes of the platelet alpha-granule protein, platelet factor 4 (PF4)-a polycation-bound to heparin-a polyanion. IgA and IgM antibodies are thought not to contribute to the pathogenesis of HIT.

**Incidence.** One to 3% of all patients exposed to unfractionated heparin (UFH) and less than 1% of patients exposed to low molecular weight heparin (LMWH) develop HIT. Fondaparinux is very rarely associated with HIT.

**Pathophysiology.** Heparin, in a molecular weight and charge dependent fashion binds to PF4 that is released from α granules of activated platelets. The Heparin-PF4 complex unveils new epitopes that generate IgG antibodies. Prior exposure to other PF4-polyanion complexes such as bacterial proteins may underlie the rapid production of IgG antibodies associated with HIT. The IgG anti-Hep-PF4 immune complex activates platelets through the FcγRIIa (CD32) receptor. Activated platelets release additional PF4 and procoagulant microparticles that activate additional platelets, attract white blood cells, promote thrombin generation and clot formation. Platelet-leukocyte-endothelial aggregates generate HIT-specific thrombosis (“white clot”).

**Clinical characteristics.** Based on the time of onset, HIT is divided into three categories: 1) typical onset (70% of cases) in which platelets drop 5 – 10 days after starting heparin therapy, 2) rapid onset (25 – 30% of cases) in which platelets drop within 24 hours of starting heparin therapy, and 3) delayed onset (rare) in which platelets drop up to 3 weeks after heparin therapy has been stopped. Patients with rapid-onset HIT have pre-formed heparin-PF4 antibodies due to recent heparin exposure, usually within the past few weeks. The platelet count falls quickly because the patient already has circulating HIT antibodies.

HIT/T is more common in surgical (orthopedics and cardiothoracic) patients than medical patients. Obstetrics and pediatrics patients for unclear reasons have a much lower incidence of HIT. HIT/T is more common in women than men. HIT/T is a strong risk factor for both venous (DVT, PE, cerebral dural sinus thrombosis, adrenal hemorrhagic infarction) and arterial thrombosis (aortic occlusion, acute thrombotic stroke, MI, cardiac intraventricular thrombosis, upper and lower limb arterial thrombosis, and mesenteric, renal, and spinal artery thrombosis). Digital/extremity gangrene is a classic presentation of HIT/T.

**Diagnosis.** The diagnosis of HIT requires consideration of its clinical and laboratory features. Reliance solely on clinical or laboratory findings invites misdiagnosis and errors in management. Therefore, a clinical assessment of the likelihood of disease is essential for accurate interpretation of laboratory test results. Lo et al. developed the first widely used and validated HIT pre-test probability model, the “4T score”, which consists of the following components:

- **Thrombocytopenia score:** >50% platelet decrease to nadir ≥20×10^9/L=2 points; 30 – 50% platelet decrease or nadir 10 – 19×10^9/L=1 point; <30% platelet decrease or nadir <10×10^9/L=0 points
- **Timing of platelet count decrease or thrombosis relative to initiation of heparin therapy score:** 5 – 10 days or ≤1 day (heparin exposure within 5 – 30 days) onset=2 points; unclear or ≤1 day (heparin exposure within 31 – 100 days) ≥10 days=1 point; ≤4 days without heparin exposure = 0 points
- **Thrombosis (venous, arterial, or skin lesions) score:** proven thrombosis or skin necrosis or anaphylactic reaction after heparin bolus =2 points; progressive or recurrent or suspected thrombosis or erythematosus skin reaction =1 point; none =0 points
- **Other potential etiologies of thrombocytopenia score:** no other explanation =2 points; other potential causes =1 point; other definite cause (sepsis; DIC; other drugs, e.g., vancomycin, sulfia, etc. =0 points

The pretest probability of HIT is high if the 4T score is ≥6 – 8 points; intermediate if the score is 4 – 5 points; and if the score is 0 – 3 points. The 4T score has been found to be useful in ICU patients with thrombocytopenia. Recently, Cuker and colleagues have proposed a new pre-test probability model, the HIT Expert Probability (HEP) model which appears to have superior diagnostic performance to the 4T score. Further validation of these pre-test probability models in different patient populations is warranted.

In addition to clinical manifestations, there are laboratory tests, which help to confirm the diagnosis of HIT. It is very important to note that the results of these tests are most informative if they are not dichotomized as being either positive or negative. Based on the value of each test a likelihood ratio (LR) for the presence of HIT can be calculated. The two most frequently used assays for diagnosis including the Heparin-PF4 antibody enzyme linked immunosorbent assay (ELISA) and the serotonin release assay (SRA).

The ELISA is performed using microtiter well plates containing immobilized PF4. Patient serum samples are added to individual wells followed by an alkaline phosphatase-linked secondary antibody that generates a colored product that can be quantified by spectrophotometer. The amount of PF4 antibody present in the patient sample correlates directly with the optical density (OD) units reported by the spectrophotometer. The ELISA has high sensitivity (99%) but relatively low specificity (80%); the specificity of the test may be improved by measuring only for heparin-PF4-IgG antibodies since IgA and IgM antibodies may be generated by heparin exposure but almost never cause HIT. An OD value of 1.0 and 2.0 carries a likelihood ratio (LR) of thrombosis of 5 and 20, respectively.

The SRA is performed by incubating patient serum containing PF4 antibodies to donor platelets pre-incubated 14C-serotonin and heparin. Functional PF4 antibodies will activate donor platelets in the presence of heparin resulting in release of 14C-serotonin, which can be measured in the supernatant. The SRA result is reported as the percentage release of 14C-serotonin from platelets. The SRA has high specificity (98%) but relative low specificity (80%); the specificity of the test may be improved by measuring only for heparin-PF4-IgG antibodies since IgA and IgM antibodies may be generated by heparin exposure but almost never cause HIT. An OD value of 1.0 and 2.0 carries a likelihood ratio (LR) of thrombosis of 5 and 20, respectively.

The SRA result is reported as the percentage release of 14C-serotonin from platelets. The SRA has high specificity (98%). For example an SRA of 80% release carries an LR of thrombosis of 10. Usually in practice, the SRA is used as a confirmatory test.

If there is a high clinical suspicion, treatment should be started before assay results are available and regardless of the laboratory test results. Lower and upper extremities duplex ultrasounds are generally recommended in patients suspected to have HIT/T as...
subclinical thrombosis is common and changes the duration of anticoagulation therapy.

**Treatment.** The principles of HIT management include two Do’s and two Don’ts. The two Do’s are, 1) Do stop all heparin (including LMWH and heparin administered as “flushes” and remove heparin-coated catheters), and 2) Do start an alternative anticoagulant such as a direct thrombin inhibitor (DTI). The two Don’ts include, 1) Don’t give warfarin (or another vitamin K antagonist) during the acute phase of HIT; if warfarin has already been started when HIT is diagnosed, its effects should be reversed with vitamin K, and 2) Don’t administer platelet transfusions unless clinically significant bleeding occurs.

The primary pharmacologic agents used in the treatment of HIT/T are direct thrombin inhibitors. Here we will briefly review the available agents with the note that these agents should be administered with close laboratory monitoring in conjunction with physicians familiar with their use.

**Argatroban** is a small molecule DTI with primary hepatic clearance and a half-life of 45 minutes in the presence of normal hepatic function. The initial weight-based infusion rate varies depending upon hepatic function and the presence of critical illness. In a patient with normal liver function who is not in the intensive care unit (ICU), the appropriate initial infusion rate is 2 mcg/kg/min. In the presence of moderate liver dysfunction defined as a total bilirubin ≥1.8 mg/dL or AST or ALT ≥150 Units/L or in ICU patients, the recommended initial infusion rate is 0.25 – 0.5 mcg/kg/min. In the presence of severe liver dysfunction defined as a total bilirubin >3.6 mg/dL or an AST or ALT >600 Units/L, argatroban should be avoided and lepirudin or bivalirudin should be considered. An activated partial thromboplastin time (aPTT) should be measured 4 hours after the initiation of therapy and after each dose adjustment. Infusion rates should be increased 10 – 25% for subtherapeutic aPTT values while supratherapeutic aPTT values should prompt dose reductions of 25 – 50%. Once a stable infusion rate is reached, the aPTT should be measured at least daily. The therapeutic aPTT range for argatroban treatment is 1.5 to 3 times the baseline value. Argatroban therapy is associated with a 6 – 7% risk of major bleeding. Argatroban also prolongs the prothrombin time-International Normalized Ratio (PT-INR), which complicates the transition to warfarin therapy. Warfarin should not be started until the platelet count has normalized. As with heparin and low molecular weight heparin, the transition from argatroban to warfarin therapy should last at least 5 – 7 days to ensure that vitamin K dependent factor activity levels have fallen sufficiently to prevent recurrent thrombosis. Since argatroban also increases the INR, an INR of 4 or more should be attained during warfarin co-therapy before argatroban is discontinued to ensure a therapeutic INR after argatroban discontinuation.

**Lepirudin** is a recombinant version of hirudin, the DTI derived from the medicinal leech. Lepirudin has renal clearance with a half-life of 80 minutes in the presence of normal renal function. Although the original package insert recommended an initial intravenous bolus of 0.4 mg/kg followed by a continuous infusion of 0.15 mg/kg/hr, excessive bleeding associated with this regimen has prompted recent recommendations to avoid bolus dosing of lepirudin. Table 1 summarizes the initial dose of lepirudin based on creatinine clearance (CrCl).

In patients with combined renal and hepatic failure, bivalirudin should be considered. An aPTT should be measured 6 hours after initiation of lepirudin and after each dose adjustment. Subtherapeutic aPTT values should prompt dose increases not more than 20% while a 50% dose decrease is appropriate for supratherapeutic values. Once stable, the aPTT should be measured at least daily. The therapeutic aPTT range for lepirudin is between 1.5 to 2.0 times the baseline value. A baseline PT/INR should be checked before transition to warfarin. In clinical trials of lepirudin there was a 17 – 18% incidence of major bleeding at therapeutic dose. Anti-lepirudin antibodies develop in up to 44% of the patients. These antibodies generally increase the circulating half-life of lepirudin so reductions in the infusion rate are often necessary.

**Bivalirudin** is a synthetic protein with reversible direct antithrombin activity that consists of the active site and fibrinogen binding site moieties of hirudin joined by a polypeptide linker. Bivalirudin has both enzymatic (80%) and renal (20%) clearance with a half-life of 25 minutes in the presence of normal renal function. The recommended initial infusion rates of bivalirudin based on CrCl are summarized in Table 2.

The aPTT should be measured 2 hours after initiation and after each dose adjustment. Dose adjustments must not be more than a 20% dose increase or 50% dose decrease. Once stable, the aPTT should be measured at least daily. The therapeutic aPTT ranges

### Table 1. Lepirudin initial dose based on estimated creatinine clearance.

<table>
<thead>
<tr>
<th>Estimated creatinine clearance (milliliter per minute [mL/min])</th>
<th>Lepirudin initial infusion rate (milligram per kilogram per hour [mg/Kg/hr])</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>0.1</td>
</tr>
<tr>
<td>45 – 60</td>
<td>0.05</td>
</tr>
<tr>
<td>31 – 44</td>
<td>0.03</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Lepirudin should be avoided</td>
</tr>
</tbody>
</table>

### Table 2. Bivalirudin initial dose based on estimated creatinine clearance.

<table>
<thead>
<tr>
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<td>45 – 60</td>
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</tr>
<tr>
<td>31 – 44</td>
<td>0.075</td>
</tr>
<tr>
<td>&lt;30 and no renal replacement therapy</td>
<td>0.05</td>
</tr>
<tr>
<td>renal replacement therapy (i.e. dialysis) or combined hepatic/renal failure</td>
<td>0.03</td>
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</table>
between 1.5 to 2.5 times the baseline value. A baseline PT should be checked before transition to warfarin. Bivalirudin therapy is associated with a 2 – 3% risk of major bleeding.

**Prognosis.** Without treatment the mortality of HIT/T is 20 – 25% with a similar percentage of patients surviving with major complications (e.g., stroke or limb loss). Early diagnosis and treatment has improved mortality and morbidity to 5 – 10%.

**Antiphospholipid antibody syndrome**

The antiphospholipid syndrome (APS) is an acquired, usually severe, autoimmune thrombophilic disorder.

**Diagnosis.** The initial international diagnostic criteria (Sapporo Criteria)\(^{23}\) for APS were revised in 2006 and a new international consensus statement with updated criteria for definite antiphospholipid syndrome were proposed.\(^{24,25}\) Based on the revised criteria, APS is present if at least one of the clinical criteria and one of the laboratory criteria from Table 3 are met.

Diagnosis of APS cannot be confirmed if less than 12 weeks or more than 5 years separate the positive anti-phospholipid (aPL) test and the clinical manifestations. Coexisting inherited or acquired factors for thrombosis should not be reasons for excluding APS. Two subcategories of APS patients should be recognized, according to the presence and the absence of additional risk factors for thrombosis. Older age (>55 years in men, and >65 years in women), and the presence of any established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥30 kg/m\(^2\), microalbuminuria, estimated GFR <60 mL/min), inherited thrombophilia, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery should be taken into account to stratify APS patients for further management of thrombosis.

APS is associated with significant morbidity and mortality with arterial and venous thrombotic events and pregnancy loss. Here we separately review the treatment strategies for venous and arterial thromboses.

**Therapy of venous thromboembolism in patients with APS.** The primary treatment for VTE due to APS is anticoagulation. However, important questions are the intensity and the duration of anticoagulation. Two randomized clinical trials,\(^{26,27}\) in contrast to previous retrospective studies,\(^{28,29}\) showed that high-intensity anticoagulation (INR between 3 to 4) was not superior to moderate-intensity (INR between 2 to 3) therapy. The incidence rates of major bleeding were similar between the two groups in both studies. When the data from both studies were pooled, it suggested that high intensity treatment is associated with an increased risk of minor bleeding complications.\(^{30}\)

Patients with VTE and positive IgG anticardiolipin testing who discontinued anticoagulants at 6 months had higher rates of recurrent VTE and death compared with patients without anticardiolipin antibodies who were treated for the same duration. Most recurrences tended to occur within the first 6 months of cessation of anticoagulation.\(^{35}\) In patients with a triggered episode of VTE and

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**Table 3. Diagnostic criteria for antiphospholipid syndrome.**\(^{24,25}\)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definitions</th>
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<tbody>
<tr>
<td><strong>Clinical criteria</strong></td>
<td></td>
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<tr>
<td>Vascular events</td>
<td>One or more objectively confirmed symptomatic episodes of arterial, venous or small vessel thrombosis. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology) and no alternative diagnosis or cause of thrombosis. Histopathologic specimens must demonstrate thrombosis in the absence of vessel wall inflammation to qualify. Superficial venous thrombosis is not included in the clinical criteria.</td>
</tr>
<tr>
<td>Pregnancy morbidity</td>
<td>One or more unexplained fetal deaths at or beyond the 10(^{th}) week of pregnancy with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or One or more premature births of a morphologically normal neonate before the 34(^{th}) week of pregnancy due to eclampsia or severe preeclampsia (defined according to standard definitions) or placental insufficiency (1), or Three or more unexplained consecutive spontaneous abortions before the 10(^{th}) week of gestation in the absence of maternal anatomic, chromosomal, or hormonal abnormalities or paternal chromosomal abnormalities</td>
</tr>
<tr>
<td>Laboratory criteria</td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>Positive test for a lupus anticoagulant (2) using a phospholipid-dependent clotting assay (aPTT, dilute Russell Viper venom assay, Kaolin clotting time, dilute PT) with evidence of phospholipid dependence present on two or more occasions at least 12 weeks apart</td>
</tr>
<tr>
<td>Anticardiolipin antibody</td>
<td>IgG or IgM Anticardiolipin antibody measured using a standardized ELISA that is present in medium or high titer (i.e. &gt;40 GPL or MPL, or &gt;99(^{th}) percentile), on two or more occasions, at least 12 weeks apart(^{26,28})</td>
</tr>
<tr>
<td>Beta2 Glycoprotein 1 antibody</td>
<td>Anti-Beta-2 glycoprotein-I IgG or IgM antibody measured using a standardized ELISA that is present in high titer (&gt;99(^{th}) percentile), on two or more occasions at least 12 weeks apart(^{29})</td>
</tr>
</tbody>
</table>

(1) Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance tests, e.g., a non-reactive non-stress test, suggestive of fetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g., absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, e.g., an amniotic fluid index of 5 cm or less, or (iv) a postnatal birth weight less than the 10\(^{th}\) percentile for the gestational age.

(2) Lupus anticoagulant (LA) should be detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on Lupus anticoagulants / phospholipid-dependent antibodies)\(^{30,31}\)
positive testing for APS, it is recommended to treat with anticoagulation for a duration of 3 months.36

**Therapy of arterial thromboembolism in patients with APS.** Stroke is a major arterial complication of APS. The only randomized clinical trial, which assessed the significance of antiphospholipid antibodies in the setting of non-cardioembolic stroke, was the antiphospholipid antibodies and stroke study (APASS).37 The study demonstrated that patients who had an initial stroke and were test positive for a lupus anticoagulant or antiphospholipid antibodies, or both, within 30 days of the event, did not have a different prognosis than those who were test negative when treated either with aspirin (325 mg daily) or low-moderate intensity anticoagulation (INR between 1.4 to 2.8) during 2 years of follow up. However, it is important to note that this study only tested patients for APS on one occasion and the threshold for antiphospholipid antibody positivity was lower than recommended in the Sapporo criteria. Therefore, the conclusion that aspirin and low-moderate intensity anticoagulation are of equal efficacy in stroke prevention must be tempered by the inherent weaknesses of this study’s design. Until further studies are conducted in patients with APS and arterial thromboembolism, aspirin or moderate intensity (INR 2-3) warfarin should be used for treatment on a case-by-case basis although the authors tend to favor anticoagulation for most APS patients with thromboembolism in light of the pro-thrombotic nature of APS.36

If the decision is made to treat the patient with aspirin, then adding a second anti-platelet agent such as dipyridamole should be considered. General population data showed that aspirin (30 – 325 mg) plus extended-release dipyridamole (200 mg twice daily) is superior to aspirin alone for secondary prophylaxis in the setting of non-cardioembolic stroke, and clopidogrel (75 mg) is as effective as aspirin plus dipyridamole in the same population.38 Clopidogrel (75 mg) alone is more effective for secondary prophylaxis than aspirin (325 mg) alone in patients who have had a previous myocardial infarction or a stroke.40

The combination of aspirin (75 – 100 mg) plus clopidogrel (75 mg) is superior to aspirin alone in preventing major vascular events in the setting of atrial fibrillation,41 though warfarin (INR 2-3) is superior to dual anti-platelet therapy.42 For secondary prevention of non-cardioembolic ischemic stroke or TIA, the combination of aspirin (75 mg) and clopidogrel (75 mg) is not superior to clopidogrel alone.43

The most important complication of anti-platelet agents and anticoagulants is bleeding. The annual incidence of major bleeding for agents used in secondary stroke prophylaxis are as follows:44 aspirin alone (<325 mg), 1%; clopidogrel, 0.85%; aspirin plus extended release dipyridamole, 0.93%; aspirin plus clopidogre, 1.7%; and anticoagulation (INR 2-3), 2.5%. Combining aspirin with warfarin significantly increases the risk of major bleeding to 3.9%, without improving protection against stroke in the setting of atrial fibrillation.45 Doses of aspirin 100 mg or greater when used in combination with clopidogrel may increase the bleeding risk, without improving protection.46

Administration of aspirin within 48 hours after an acute (non-cardioembolic or cardioembolic) stroke in the general population resulted in a significant reduction of 0.7% in recurrent ischemic stroke (1.6% aspirin vs. 2.3% control, P=0.000001) and a borderline reduction of 0.4% in death without further stroke (5.0% vs. 5.4%, P=0.05). There was an increase of 0.2% in hemorrhagic stroke or hemorrhagic transformation of the original infarct (1.0% vs. 0.8%, P=0.07) and no apparent effect on further stroke of unknown cause (0.9% versus 0.9%). In summary there was a net decrease of 0.9% in the overall risk of further stroke or death in hospital (8.2% vs. 9.1%, P=0.001). The absolute risk among control patients was similar in all subgroups, so the absolute reduction of approximately 0.7% in recurrent ischemic stroke does not differ substantially with respect to age, sex, level of consciousness, atrial fibrillation, CT findings, blood pressure, stroke subtype, or concomitant heparin use.47

On the other hand, anticoagulation, either with UFH, LMWH, oral anticoagulants, or thrombin inhibitors, within the first 48 hours of an acute (non-cardioembolic or cardioembolic) stroke did not reduce the odds of death or dependency in two meta-analyses but was associated with an increased risk of hemorrhagic transformation.48,49 It is important to distinguish this finding with the clear advantage of oral anticoagulation (started within 3 months) over aspirin for long-term secondary stroke prophylaxis after a minor stroke or TIA associated with APS.

These findings all together suggest that if a decision to implement secondary thromboprophylaxis with oral anticoagulation after a stroke is made, it is reasonable to initiate it after the acute period (at least 48 hours) during which time aspirin should be used.36 If there is evidence of a substantial mass effect or well-defined hypodensity involving greater than one-third of the middle cerebral artery territory on CT scan or MRI, then it may be prudent to delay the start of oral anticoagulation for 2 weeks or more considering the elevated risk of spontaneous hemorrhagic transformation associated with large infarcts.50

In spite of recommendation by some experts, randomized clinical trials have not yet adequately evaluated the use of early, full therapeutic doses of heparin in some specific stroke subgroups, such as atrial fibrillation with rheumatic heart disease, prosthetic heart valves, or intracardiac thrombus, against the theoretical risk of hemorrhage.51 Until more definite data become available the decision for beginning heparin depends on the size and stability of the intracardiac thrombus, the size of the cerebral infarct, and the presence or absence of uncontrolled hypertension. A large, unstable intracardiac thrombus on the echocardiogram, a small stroke or TIA (and exclusion of hemorrhage) on CT or MRI, and well controlled blood pressure perhaps will justify considering using adjusted-dose heparin early, followed by long-term, oral anticoagulation.52

It may be pertinent to mention that the risk of hypercoagulability aggravation after commencing vitamin K antagonists may be greater in APS patients because of the functional impairment of the protein C system, likely related to anti-βGPI autoantibodies with lupus anticoagulant activity.53,54 This may further justify the use of full-dose heparin initially in the stroke patients with βGPI antibodies.

It is generally accepted to treat non-cerebral artery thrombosis in locations such as the renal arteries or other intraabdominal arteries with moderate-intensity oral anticoagulation indefinitely.

**Recurrent venous or arterial thromboembolism in patients with APS.** Recurrent VTE or ATE in patients with APS after cessation of anticoagulation dictate reinstitution of therapeutic anticoagulation (INR 2-3) of indefinite duration. Regular therapeutic monitoring is essential for optimal outcomes.36

If venous or arterial thromboembolism recurs during vitamin K antagonist therapy (INR 2-3), after confirmation therapeutic INR goal and patient adherence, we recommend strong consideration...
of high intensity (INR 3 to 4) or initiation of low molecular weight heparin therapy. If arterial thrombosis occurred while the patient is on moderate-intensity anticoagulation (and the therapeutic range is confirmed), then addition of low-dose aspirin (≤100 mg/day) should be considered. Unfortunately, the evidence basis for these recommendations is limited to small observational studies.

LMWH should also be considered in patients who are difficult to maintain in the therapeutic range during vitamin K antagonist therapy. The comparable efficacy and safety of long-term LMWH compared with oral anticoagulation for prevention of recurrent VTE has been confirmed in a meta-analysis.57 However, vitamin K antagonists remain the treatment of choice for the majority of patients because of their oral route of administration and low acquisition cost. The importance of maintaining good control of the INR within the therapeutic range to prevent thrombotic recurrences and bleeding complications has been confirmed in a variety of different clinical scenarios.58,59 Addition of low-dose vitamin K supplementation (100 – 150 micrograms daily) has been shown to improve INR control.60 Therefore, this strategy is also worthy of consideration in patients with recurrent events and suboptimal time in the therapeutic range.

The advent of several new direct oral anticoagulants including dabigatran, rivaroxaban, and apixaban raises the hope that these therapies may also improve INR control.60 Therefore, this strategy is also worthy of consideration in patients with recurrent events and suboptimal time in the therapeutic range.

Catastrophic antiphospholipid syndrome61,62
Catastrophic antiphospholipid syndrome (CAPS) is a rare (<1%) of APS patients present with CAPS life-threatening manifestation of APS characterized by multi-organ (kidneys, brain, skin, liver, etc.) failure resulting from diffuse microvascular thrombosis. CAPS is often triggered in APS patients by infections, major surgery, discontinuation of immunosuppression, or anticoagulation. Half of CAPS patients do not have underlying autoimmune diseases (e.g., systemic lupus erythematosus).

Almost all patients with CAPS require ICU level of care. Organ involvement in CAPS is summarized in Table 4.4,53

Pathophysiology: Potential causal mechanisms of CAPS include, endothelial cell damage or activation by APL or APL-induced monocyte adherence to endothelial cells, anti-endothelial antibodies, platelet activation by APL binding to platelet membrane phospholipid-bound annexins, interference with activated protein C, increased monocyte and endothelial cell tissue factor (TF) activity, induction of nuclear factor (NF)-κB translocation by anti-β2-GPI binding leading to a pro-inflammatory endothelial cell phenotype, and production of pro-inflammatory cytokines (IL-1β and TNF-α).

Risk factors: HLA-DMA 0102 is considered to be a genetic risk factor for the production of APL. Val (247) β2-GPI allele is known as a risk factor for the production of β2-GPI antibodies.

Diagnosis. CAPS diagnosis is based on International Classification Criteria, which are shown in Table 5.

Table 4. Clinical manifestations of the catastrophic antiphospholipid syndrome.

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Coombs positive hemolytic anemia, autoimmune thrombocytopenia, DIC, bone marrow infarct</td>
</tr>
<tr>
<td>Brain</td>
<td>Infarcts, encephalopathy, seizure, transient ischemic attack (TIA)</td>
</tr>
<tr>
<td>Heart</td>
<td>Valvular lesions (Libman-Sacks endocarditis), myocardial infarction, heart failure</td>
</tr>
<tr>
<td>Kidney</td>
<td>A 50% increase in serum creatinine, severe systemic hypertension (&gt;180/100 mm Hg), and/or proteinuria (&gt;500 mg/24 hr)</td>
</tr>
<tr>
<td>Lung</td>
<td>Acute respiratory distress syndrome (ARDS): most common, pulmonary hypertension with normal cardiac output and pulmonary capillary wedge pressure, pulmonary hemorrhage</td>
</tr>
<tr>
<td>Skin</td>
<td>Livedo reticularis, skin ulcers, digital ischemia, purpura, skin necrosis</td>
</tr>
<tr>
<td>Vasculature</td>
<td>Venous and/or arterial thromboembolism: most common include deep venous thrombosis, pulmonary embolism, extremity artery thromboembolism, portal vein, and inferior vena cava thrombosis, retinal artery and vein thrombosis</td>
</tr>
</tbody>
</table>

Table 5. Diagnostic criteria for catastrophic antiphospholipid syndrome.65

1. Evidence of involvement (vascular occlusions) affecting 3 or more organs, systems, and/or tissues (a)
2. Development of manifestations simultaneously or within 1 week or less
3. Confirmation by histopathology of small vessel occlusion in one organ or tissue (b)
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibodies) (IgG/IgM anti-cardiolipin (>40 GPL or MPL units) or anti-β2-glycoprotein I antibodies (>99th percentile) or positive lupus inhibitor on coagulation testing) (c)

Definite catastrophic antiphospholipid syndrome
All four criteria are met

Probable Catastrophic Antiphospholipid Syndrome
All four criteria are present but only 2 organs, systems, or tissues are involved
All four criteria are present but confirmation of laboratory tests 6 weeks apart not performed
Criteria 1, 2, and 4 are present
Criteria 1, 3, and 4 are present

(a) Objective evidence of vessel occlusions. A 50% rise in serum creatinine, severe systemic hypertension (>180/100 mmHg) and/or significant proteinuria (>500 mg/24 hours) are alternative manifestations of renal involvement. (b) Thrombosis must be present on histopathology. Vasculitis may be present but is not diagnostic in isolation. (c) If the patient has not had previous laboratory testing for APS, then laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least 12 weeks apart (not necessarily at the time of the event).
The differential diagnosis includes severe sepsis, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC), infectious purpura fulminans (IPF), and HIT/T.

Treatment of CAPS requires a multi-modality approach that targets potential precipitating factors including measures such as broad spectrum antibiotics for infections, aggressive hemodynamic resuscitation in the case of shock, debridement or amputation for necrotic tissues, mechanical ventilation, renal replacement therapy, tight glycemic control, stomach acid suppression, and control of malignant hypertension in case of renal artery/vein thrombosis. Intravascular instrumentation, especially arterial, should be minimized because of the potential to induce new clots.

First-line therapies for CAPS include anticoagulation usually with UFH (start with 50–80 units/Kg bolus, followed by 14–18 units/Kg/hr) initially followed by warfarin (INR 2-3) once the patient is stabilized. CAPS is usually refractory to anticoagulation alone, hence, corticosteroids is a major modality of treatment aimed at limiting NF-kB activation and down-regulating production of inflammatory mediators. IV pulse methylprednisolone (1000 mg per day) for 3 to 5 days followed 1 – 2 mg/kg/d is the most commonly administered regimen.

Second-line therapies are frequently necessary in the absence of a clinical response or ongoing thrombosis despite first-line treatment. Intravenous immunoglobulins (IVIG) is commonly used for this indication with several potential mechanisms of action including interference with APL antibody activity. The usual dose of IVIG is 2 g/Kg (400 mg/Kg for 5 days or 1000 mg/Kg for 2 days). In patients at risk for IVIG-associated renal toxicity (diabetes mellitus, pre-existing renal insufficiency, older age), non-sucrose containing products and lower dose intensity regimens should be used. Due to severe anaphylactic reactions, IVIG is contraindicated in patients with IgA deficiency (rare). Plasmapheresis is another therapeutic option. The mechanism of action is thought to be removal of pathogenic antibodies and cytokines. GPI levels can be used as a marker of response to plasma exchange. It is unclear whether plasma exchange or IVIG is superior.

Third-line treatments includes, 1) fibrinolytics agents such as alteplase for life- or limb threatening venous or arterial thrombosis, 2) cyclophosphamide-multiple dosage protocols, 3) prostacyclin: teplase for life- or limb threatening venous or arterial thrombosis, or IVIG is superior. As a marker of response to plasma exchange. It is unclear whether platelet counts or other coagulation parameters may be useful. The mechanism of action is thought to be removal of pathogenic antibodies and cytokines. GPIIb/IIIa levels can be used as a marker of response to plasma exchange. It is unclear whether plasma exchange or IVIG is superior.

Prognosis. CAPS mortality rate remains as high as 48% despite all therapies. The clinical manifestations associated with a poor prognosis and increased mortality include renal involvement, splenic involvement, pulmonary involvement, adrenal involvement, and SLE diagnosis. CAPS recurrence is unusual. Patients usually have a stable course with continued anticoagulation. One fourth of the survivors will develop further APS-related events, but it is rare to develop recurrent CAPS.

Thrombohemorrhagic events in myeloproliferative neoplasms

Philadelphia chromosome-negative chronic myeloproliferative neoplasms (MPN) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). They share overlapping clinical features, albeit exhibit different natural histories and may have different therapeutic requirements. JAK2-V617F is a somatic gain-of-function mutation, which involves the JAK2 tyrosine kinase gene and occurs with variable frequency in MPN as assessed on peripheral blood. JAK2-V617F occurs in >90% of PV, approximately 50% of ET and MF, <20% of atypical myeloproliferative neoplasms, <5% of myelodysplastic syndrome (MDS), and does not occur in chronic myelogenous leukemia (CML). Expression of JAK2-V617F mutation establishes the presence of an MPN but does not distinguish between the different types (i.e., PV vs. ET). Absence of JAK2 V617F does not exclude MPN.

Epidemiology. PV has an annual incidence of 2 per 100,000 population with a median age of 70 years. At initial presentation, the prevalence of thrombosis and bleeding are 12 – 39% and 2 – 20%, respectively. ET has an annual incidence of 0.5 – 2.5 per 100,000 population with a median age of 60 years. The incidence of thrombosis and bleeding in ET has been reported to be 6.6% per patient-year and 0.33% per patient-year, respectively.

Clinical Features. Thrombosis in PV and ET occurs in arterial, venous, or microcirculation with large vessel arterial events including cerebrovascular accidents (stroke and transient ischemic attacks), myocardial infarction, and peripheral arterial occlusion being the predominant cause of morbidity and mortality. Lower extremity DVT and PE account for the majority of venous events. Intra-abdominal (portal and hepatic) vein thrombosis is characteristic of MPNs, particularly in young women with PV, and accounts for a substantial proportion of catastrophic events. In one study, the underlying MPN was shown to be responsible for 30 – 50% of unexplained (without cirrhosis or hepatobiliary carcinoma) portal or hepatic vein thrombosis. Headache, paraesthesias, and erythromelalgia as manifestations of microcirculation problems are common in ET and PV. Erythromelalgia is a microvascular thrombotic syndrome, which presents with unilateral or bilateral asymmetric erythema, congestion, and burning pain of the hands and feet. Without treatment, it may progress to acrocyanotic ischemia and gangrene. Usually symptoms resolve promptly with aspirin.

Although, bleeding episodes in PV and ET can be severe and require hospitalization and blood transfusion, it primarily involves skin and mucous membranes suggesting defective primary hemostasis. Gastrointestinal bleeding is less frequent and is often associated with aspirin use. In patients with extreme thrombocytosis (platelets >1,000,000/µL) and bleeding symptoms it is important to look for acquired von Willebrand disease. One study noted acquired von Willebrand disease in 11% of MPN patients. Acquired von Willebrand disease in MPN patients typically has a type 2a phenotype with loss of large and intermediate von Willebrand factor multimers due to adhesion of large molecular weight vWF multimers to abnormal MPN platelets or digestion of large multimers due to proteases derived from MPN platelets. Diagnosis rests upon measurement of aPTT, PT, platelet count, von Willebrand factor antigen and activity levels (e.g., ristocetin cofactor assay or collagen binding assay), factor VIII activity and von Willebrand factor multimer analysis. Platelet cytoprotection can be effective in improving acquired von Willebrand disease in MPN patients.

Surgical procedures can be associated with morbidity and mortality in MPN due to both thrombosis and hemorrhage. Risks particularly are high when the underlying disease (erythrocytosis in PV or thrombocytosis in both PV and ET) is not well-controlled.
**Pathophysiology.** Different MPNs share the following common features: overproduction of one or more of the elements of the blood in the absence of a defined stimulus with hypercellular bone marrow, chromosomes 1, 8, 9, 13, and 20 abnormalities, thrombotic and/or hemorrhagic events, leukemic transformation, and the development of narrow fibrosis.

Pathogenesis of thrombohemorrhagic events in PV and ET is multifactorial including erythrocytosis, thrombocytosis, functional and structural platelet abnormalities, platelet membrane receptor abnormalities, leukocyte activation, and acquired von Willebrand syndrome. Risk factors for development of thrombohemorrhagic events in PV and ET are comprised of age >65 years, previous history of thrombotic events, poorly controlled erythrocytosis, presence of leucocytosis, thrombocytocemia, concurrent thrombophila (hereditary or acquired), monoclonal X-chromosome inactiva
tion (ET), and cardiovascular risk factors including hypertension, smoking, hypercholesterolemia, and diabetes mellitus.

**Diagnosis.** There are at least three sets of criteria proposed for diagnosis of PV and ET.64,82,27 Table 6 demonstrates the criteria proposed by Spivak and Silver.64 In this, bone marrow examination or assays for erythropoietin and erythroid colony-forming cells are not part of the diagnostic criteria.

MPN-related thromboses can be diagnosed with brain magnetic resonance angiography (MRA) or magnetic resonance venography (MRV), CT-angiography, duplex ultrasound and coronary angiography, depending on the suspected location of the thrombosis. Any persistent abdominal pain requires contrast CT scan of hepatic, portal and mesenteric veins in a patient with a history of MPN.

**Treatment.** Appropriate management of acute venous or arterial thrombosis in patients with MPN requires consideration of the presence or absence of situational thrombotic triggers and an assessment of the adequacy of therapeutic control of the underlying MPN.

In PV patients, it is important to assess whether there is suboptimal control of erythrocytosis as increasing hematocrit is historically thought to be associated with an increasing risk of thrombo
sis.24,45 In men, the hematocrit should be maintained below 45%, in women below 42%. In patients with well controlled erythrocytosis, lower hematocrit targets or cytoreductive therapy (e.g., hydroxyurea, α-interferon) should be considered. Since hydroxyurea appears to be associated with an increased risk of leukemic transforma
tion in MPN patients, it is important to carefully consider its risks and benefits before initiating therapy.26 In patients with ve
nous thromboembolism, conventional anticoagulation consisting of acute therapy with a parenteral anticoagulant followed by long-
term therapy with a vitamin K antagonist is appropriate. Although LMWH has been shown to be superior to VKA in cancer patients,77 it remains unclear whether these benefits extend to patients with MPN. The presence or absence of situational thrombotic triggers should be considered to determine the appropriate duration of antithrombotic therapy. Unless a strong situational trigger (i.e., surgery) was present, long-term therapy should be considered given the ongoing presence of the MPN. Of course, the risk of bleeding must also be factored into this decision. A similar approach is warr
anted in patients with arterial thromboembolism except that antiplatelet agents are the mainstay of anti-thrombotic therapy.

We recommend a similar approach in patients with ET. The thrombotic event should be treated in a conventional fashion and an assessment of MPN disease control is necessary. In ET, WBC counts are more tightly linked to thromboembolism than platelet counts, therefore cytoreductive therapy should be considered in patients with leucocytosis with the goal of reducing WBC in addi
tion to vascular territory specific anti-thrombotic therapy (e.g., anti-platelet agents for arterial thromboembolism, anticoagulants for VTE). Since age is an important thromboembolic risk factor, cytoreductive therapy should be considered more strongly for pa
tients age 65 or older.

The only randomized clinical trial59 to date comparing aspirin plus either hydroxyurea (initial dose of 0.5 – 1 g/day) or anagrelide (initial dose of 0.5 mg bid) in at-risk ET patients showed fewer transient ischemic attacks in patients taking hydroxyurea. How
ever, DVT frequency was lower in the anagrelide group. No di
dference in unstable angina, myocardial infarction, stroke, arterial embolus of the lower or upper limbs, hepatic vein thrombosis or pulmonary embolism was observed. Serious hemorrhage (GI bleeding) was more frequent in anagrelide patients. The risk (po
tential leukemogenicity and myelotoxicity, especially in younger patients) and benefit ratio must be carefully reviewed with patients prior to the initiation of cytoreductive treatment. Unfortunately, this study does not provide optimal guidance for ET patients with previous thromboembolic events (particularly VTE) since a mi
ority of participants had previous thromboembolism.79

Aspirin in both ET and PV effectively controls microvascular symptoms. In patients with PV, low-dose aspirin (100 mg daily) reduces both arterial and venous thrombosis.80 ET patients with extreme thrombocytosis should be monitored carefully for hemor
rhagic effects of antiplatelet therapy and acquired von Willebrand disease. There are limited data on efficacy of other antiplatelet agents in MPNs.

**Prognosis.** Natural history of ET is compatible with a normal life span. Natural history of PV is not completely defined and neither staging criteria nor factors affecting prognosis have been

| Table 6. Diagnostic criteria: polycythemia vera and essential thrombocythemia. |
|--------------------------|--------------------------|
| **Polycythemia vera**    | **Essential thrombocythemia** |
| Elevated red cell mass and normal or elevated plasma volume | Persistent thrombocytosis >400×109/L in the absence of a reactive cause |
| Normal arterial oxygen saturation | Absence of iron deficiency (normal serum ferritin for gender) |
| Splenomegaly | Hemoglobin <16g/dL in a man or <14 g/dL in a woman in the absence of splenomegaly |
| If no splenomegaly, any 2 of the following: | Red cell mass and plasma volume normal (Determinations are mandatory if a JAK2 V617F assay is positive) |
| Leukocytosis >12×109/L | Negative Bcr-Abl FISH (peripheral blood) if a JAK2 V617F assay is negative |
| Thrombocytosis >400×109/L | If there is anemia or macrocytosis or leukopenia, or evidence of extramedullary hematopoiesis (i.e. circulating nucleated erythrocytes, immature myelocytes or splenomegaly), a bone marrow examination (including flow cytometry and cytogenetics) is mandatory regardless of JAK2 V617F expression status |
established. However, it appears that age and sex have important influence.

Paroxysmal nocturnal hemoglobinuria (PNH)

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic stem cell disorder that causes episodic intravascular hemolytic anemia, abdominal pain, esophageal spasm, fatigue, thrombosis, and bone marrow suppression. PNH can arise de novo or from acquired aplastic anemia. Thrombosis occurs in about 40% of PNH patients and predominantly involves the venous system. Patients with a large PNH clone (>50% of granulocytes affected) and classical symptoms (hemolytic anemia and hemoglobinuria) have a greater propensity for thrombosis.

Pathophysiology. The PNH stem cell and all of its progeny have a mutation in the X-linked PIG-A (phosphatidylinositol glycan class A) gene which blocks biosynthesis of cell surface glycosylphosphatidylinositol-anchored proteins (GPI-AP). GPI-APs function as enzymes, receptors, complement regulators, and adhesion molecules. PNH erythrocytes are susceptible to complement-mediated lysis because they lack membrane inhibitor of reactive lysis (CD59) and decay accelerating factor (CD55), two GPI-AP that regulate complement activation. The result is intravascular hemolysis and the release of large amounts of free hemoglobin into the plasma. Free plasma hemoglobin acts as a nitric oxide scavenger resulting in abdominal pain, esophageal spasm, and erectile dysfunction.

The etiology of thrombosis in PNH is not completely understood, but it is believed to be related to intravascular hemolysis. Nitric oxide depletion causes increased platelet aggregation, platelet adhesion, and accelerated clot formation. Platelets exocytosis, a consequence of complement-mediated membrane damage, results in externalization of phosphotidylserine and platelet microvesicle formation, changes that promote coagulation activation and thrombin generation. Perturbed fibrinolysis results from the loss of the GPI-anchored urokinase receptor. Tissue factor pathway inhibitor (TFPI), a major inhibitor of tissue factor, has been shown to require a GPI-anchored chaperone protein for trafficking to the endothelial cell surface.

Hepatic vein thrombosis (Budd-Chiari syndrome) and cerebral venous sinus thrombosis are the most common sites of thrombosis in PNH; however, all veins, especially small vessels in the abdomen are susceptible.

Diagnosis relies upon monoclonal antibodies directed against specific GPI anchored proteins. Ideally, at least two different monoclonal antibodies, directed against two different GPI anchored proteins, on at least 2 different cell lineages, should be used to diagnose PNH. Examining only red cells for PNH can lead to falsely negative tests, especially in the setting of a recent hemolytic episode or a recent blood transfusion. Since granulocytes and monocytes have a short half-life and are not affected by blood transfusions, the percentage of PNH cells in these lineages best reflects the size of the PNH clone. Anti-CD59 is most commonly used because it is widely expressed and is displayed on all hematopoietic lineages.

A fluorescein-labeled proaerolysin variant, FLAER, binds selectively and with high affinity to the glycan portion of the GPI anchor. Due to the lack of GPI anchors, PNH cells are resistant to aerolysin and proaerolysin, hence the FLAER assay gives a highly accurate assessment of the GPI anchor deficit on PNH cells. Flow cytometry measures the size of the PNH clone in the various cell lineages and is very sensitive and specific if performed on granulocytes.

Treatment. Allogeneic hematopoietic stem cell transplantation is the only curative therapy for PNH. Younger patients with severe pancytopenia or life-threatening thrombosis who have an HLA-identical sibling are the best candidates for this approach.

Eculizumab is a humanized monoclonal antibody against C5 that inhibits terminal complement activation and is the first effective drug therapy for PNH. The drug was approved by Food and Drug Administration in 2007. Since terminal complement blockade may be associated with an increased risk for Neisseria infections, all patients treated with eculizumab must be vaccinated against Neisseria meningitides before receiving the drug. In two clinical trials leading to the approval of eculizumab, hemolysis was significantly reduced leading to improved anemia with increased transfusion independence, lessened fatigue, mitigation of the smooth muscle dystonias and improved overall health-related quality of life. The thromboembolism rate with eculizumab treatment was 1.07 events/100 patient-years compared to 7.37 events/100 patient-years (P<0.001) before eculizumab treatment. This translates into an 85% absolute reduction in the risk for thrombosis while on eculizumab treatment.

It has been reported that the pre-eculizumab thromboembolic event rate remained elevated in patients treated either therapeutically or prophylactically with antithrombotics, such as warfarin, suggesting that such therapies were not adequate to prevent thromboembolic events in this patient population. By contrast, chronic administration of eculizumab, a therapy that targets the underlying hemolysis in PNH, significantly reduced the overall thromboembolic event rate. Whether anticoagulants can be reduced or eliminated in patients with PNH receiving eculizumab is the subject of future investigation. We have reported the first successful discontinuation of anticoagulation following eculizumab administration in PNH.

Chronic anticoagulation was shown to be associated with an overall risk of 7.6 bleeding complications per 100 patient-years with the risk increasing to 11.0 bleeding complications per 100 patient-years during the first 90 days of treatment. The risk for hemorrhage with anticoagulant therapy in patients with PNH has been reported to be approximately 5% or higher, including fatal hemorrhage.

Prognosis. Thrombosis is an ominous complication of PNH and the leading cause of death from the disease. The following independent factors have been reported to be related to poor survival: 1) diagnosis before 1996, 2) age ≥40 years at diagnosis, 3) hemoglobin level ≤10 g/dL at diagnosis, 4) neutropenia, 5) absence of specific treatment [no use of immunosuppressive therapy (anti-thymocyte globulin (ATG) and/or cyclosporin (CsA)], no corticosteroids, no androgens or Danazol, and no warfarin therapy during the first year, 6) severe complications occurring during follow-up such as progression to bi- or pancytopenia, 7) development of thrombosis, 8) myelodysplastic or aplastic anemia development.

Hillmen and colleagues recently reported the survival data on 79 consecutive patients treated with eculizumab between 2002 and 2010. They showed that survival of patients treated with eculizumab was significantly better than 30 similar patients managed before eculizumab (P=0.03). There was no difference in survival of patients treated with eculizumab with age- and sex-matched normal controls (P=0.46). Furthermore, they reported that 21 patients with
no previous thrombosis discontinued warfarin on ecilizumab with no thrombotic consequences.

References


