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Critical Care Clotting Catastrophies

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Most patients in ICU will develop coagulation defects [1–4]. The immediate priorities are to establish the severity of the coagulation defects, evaluate for life threatening processes, and initiate therapy.

Initial evaluation

When an ICU patient is found to have a bleeding problem, the initial assessment should focus on how serious the bleeding is and on the underlying disorders that led to the ICU admission, on current medications, and on the past medical history.

Clinical examination should seek first to determine whether the patient is suffering from a "structural" cause of localized bleeding (ie, bleeding from a gastric ulcer) or from more generalized bleeding suggesting a systemic coagulation defect. Presence of the latter may be suggested by inspection of instrumentation sites (eg, IV sites, chest tube drainage, or mucosa for bleeding). The digits should be examined for evidence of emboli or ischemia, which, if present, again suggest a systemic problem.

Exposure to medicines is a common cause of thrombocytopenia and can augment coagulation defects [5,6]. All the medicines the patient has received should be noted on the medication sheets and the family should be quizzed about medication [7–9] the patient is taking (Table 1 and Box 1).

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Table 1
Drugs and hemostasis

Action	Drug
Increasing activity of warfarin	Acetaminophen
	Allopurinol
	Amiodarone* (may last for months after drug is stopped)
	Anabolic steroids*
	Aspirin*
	Cephalosporins (NMTT group)
	Cimetidine*
	Ciprofloxacin
	Clofibrate*
	Cyclophosphamide
	Disulfiram
	Erythromycin*
	Fluconazole*
	Furosemide
	Gemfibrozil
	Isoniazid
	Itraconazole*
	Ketoconazole*
	Metronidazole*
	Micronase*
	Omeprazole
	Propafenone
	Propranolol
	Quinidine*
	Quinine*
	Quinolones
	Serotonin uptake inhibitors
	Sulfinpyrazone*
	Sulfonylureas*
	Tamoxifen*
	Tetracycline*
	Thyroid hormones*
	Tricyclics
	Vitamin E*
Decrease activity of warfarin	Alcohol
	Barbiturates*
	Carbamazepine
	Corticosteroids
	Phenytoin (may potentiate warfarin with initiation of drug)
	Cholestyramine
	Dicloxacillin
	Estrogens
	Griseofulvin
	Nafcillin
	Rifampin
	Sucralfate
	Vitamin K
Increase prothrombin time	N-methylthiotetrazole (NMTT) group containing antibiotics: cefamandole, cefoperazone, cefotetan, cefmenoxime and cefmetazole

(continued on next page)

Table 1 (*continued*)

Action	Drug
TTP/HUS	Mitomycin C, cyclosporine, FK 506, carbo- or cis-platinum, ticlopidine, clopidogrel
Hemolysis/DIC syndrome	Quinine, 2nd and 3rd generation cephalosporins
Thrombocytopenia	See Table 8

* Major effect; bold, Strongest evidence for effect.

Data from: Tiede DJ, Nishimura RA, Gastineau DA, et al. Modern management of prosthetic valve anticoagulation. Mayo Clin Proc 1998;73:665–80. Hirsh J, Dalen JE, Anderson DR, et al. Oral anticoagulants: mechanisn of action, clinical effectivenss, and optimal theraueutic range. Chest 2001; 119:8S–21S. DeLoughery TG. Anticoagulant therapy in special circumstances. Curr Cardiol Rep 2000;2:74–9.

Laboratories

The first step in laboratory evaluation of the bleeding patient is to obtain a basic set of coagulation tests consisting of a prothrombin time international normalized ratio (PT-INR), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen [10]. Three patterns of defects can be seen in the PT-INR and aPTT (Box 2). Isolated elevations of the PT-INR are indicative of an isolated factor VII deficiency. In sick patients, low factor VII levels are common because of third-spacing and increased consumption [11]. A marked elevation of the PT-INR out of proportion to the aPTT suggests vitamin K deficiency. Isolated elevation of the aPTT has many causes. Mixing studies can provide information to narrow the list of possible diagnoses. Prolongation of both the PT-INR and aPTT suggest multiple defects or deficiency of factors II, V, or X. As discussed later, marked prolongation of the PT-INR and aPTT can also be seen with low levels of fibrinogen. Additional coagulation tests can be ordered based on the PT-INR and aPTT to better define the defect if the reason for the coagulation deficiency is not apparent by the history.

If the platelet count is low, examination of the blood smear is essential to make sure that pseudothrombocytopenia [12] is not present. Examination of the blood smear is also essential to diagnose microangiopathic processes. Although many processes can cause a moderately low platelet count, the differential diagnosis for isolated profound thrombocytopenia (<10,000/uL) is usually limited to immune thrombocytopenia, drug-induced thrombocytopenia, or post-transfusion purpura (Box 3).

Excessive bleeding has been reported with plasma fibrinogen levels under 50 mg/dL [13]. Fibrinogen is also essential for the proper function of coagulation tests. Low fibrinogen levels reflect either severe liver disease, consumptive coagulopathy, or dilution by infusion of massive amounts of resuscitative fluids. There are some bleeding defects that cannot be detected by routine laboratory tests. These defects include platelet function defects or increases in fibrinolysis.

Box 1. Herbal medicines and hemostasis

Possible increase risk of bleeding

Angelica root
Horse chestnut
Arnica flower
Licorice root
Anise
Loavage root
Asafoetida
Meadowseet
Bogbean
Onion
Borage seed oil
Parsley
Bromelain
Passionflower herb
Ginkgo
Celery
Quassia
Chamomile
Red clover
Clove
Rue
Renugreek
Sweet clover
Feverfew
Turmeric
Garlic
Willow bark
Ginger
Capsicum
Poplar

Possible increase in warfarin effect

Danshen
Dong quai
Devil's claw
Papain

Possible decease in warfarin effect

Coenzyme Q10
Green tea
Ginseng

Data from: Heck AM, DeWitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. Am J Health-System Pharm 2000;57:1221–30.

Diagnostic clues

The reason for the ICU admission is an important indicator in evaluation of any coagulation defect (Tables 2 and 3) [14]. How long the patient has been in the ICU is also important. In long-term critical care patients, new onset thrombocytopenia may be a manifestation of HIT, drug induced thrombocytopenia, or bacteremia.

Transfusion therapy

The approach to transfusion therapy of the patient with coagulation defects is to measure the five laboratory tests that reflect the basic parameters essential for both blood volume and hemostasis [15,16]. These tests are:

Hematocrit
Platelet count
Prothrombin time
Activated partial thromboplastin time
Fibrinogen level

Replacement therapy is based on the results of these laboratories and the clinical situation of the patient (Box 4).

The transfusion threshold for low hematocrit depends on the stability of the patient. If the hematocrit is below 30% and the patient is bleeding or hemodynamically unstable, packed red cells should be transfused. Stable patients can tolerate lower hematocrits and an aggressive transfusion policy may be detrimental [17,18].

The "transfusion trigger" for platelets can be 10,000/uL if the patient is stable without signs of bleeding, is not on platelet inhibitors, has preserved renal function, and does not have disseminated intravascular coagulation (DIC) [19]. If one of these risk factors is present, keeping the count more than 50,000/uL is

Box 2. Interpretations of coagulation tests

Elevated prothrombin time, normal aPTT

Factor VII deficiency
Vitamin K deficiency
Warfarin
Sepsis
DIC (occasionally)

Normal prothrombin time, elevated aPTT

Isolated factor deficiency (VIII, IX, XI, XII, contact pathway proteins)
Specific factor inhibitor
Heparin
Lupus inhibitor

Elevated prothrombin time, elevated aPTT

Multiple coagulation factor deficiencies
Dilutional effect
Liver disease
Disseminated intravascular coagulation
Isolated factor X, V or II deficiency
Factor V inhibitors
High hematocrits (>60% - spurious)
High heparin levels
Severe vitamin K deficiency
Low fibrinogen (<50 mg/dL)
Dysfibrinogemia

reasonable [15,20]. The dose of platelets to be transfused should be 6–8 platelet concentrates or one plateletpheresis unit.

For a fibrinogen level <100–125 mg/dL, transfusions of 10 units of cryoprecipitate should increase the plasma fibrinogen level by 100 mg/dl.

In patients with an INR >1.6–2.0 and an abnormal aPTT, fresh frozen plasma (FFP) is given with the dose, dependent on the aPTT. For an aPTT >1.5 times normal, 2–4 units of plasma should be given. Elevation of the aPTT >1.8 times normal is associated with bleeding in trauma patients [13]. Patients with marked abnormalities such as an aPTT >2 times normal may require aggressive therapy of at least 15–30ml/kg (4–8 units for an average adult) of plasma [21].

Box 3. Typical platelet counts in various disease states

Moderate thrombocytopenia (50–100,000/uL)

Thrombotic thrombocytopenic purpura (TTP)
Heparin induced thrombocytopenia (HIT)
Disseminated intravascular coagulation (DIC)
Hemophagocytic syndrome
Liver disease/ hypersplenism

Severe thrombocytopenia (<20,000/uL)

Drug induced thrombocytopenia
Post-transfusion purpura
Immune thrombocytopenia (ITP)
Heparin induced thrombocytopenia (unusual)
Thrombotic thrombocytopenic purpura (less common)

The basic five laboratory tests should be repeated after administering the blood products. This insures adequate replacement therapy was given for the coagulation defects. Frequent checks of the coagulation tests also allow rapid identification and therapy of new coagulation defects in a timely fashion. A flow chart of the test and the blood products administered should also be maintained.

Table 2
Diagnostic clues to thrombocytopenia

Clinical setting	Differential diagnoses
Cardiac surgery	Cardiopulmonary bypass, HIT, dilutional thrombocytopenia, heart valve hemolysis
Interventional cardiac procedure	Glycoprotein IIb/IIIa blockers, HIT
Sepsis syndrome	DIC, ehrlichiosis, Sepsis hemophagocytosis syndrome, drug-induced, misdiagnosed TTP, mechanical ventilation, pulmonary artery catheters
Pulmonary failure	DIC, hantavirus pulmonary syndrome, mechanical ventilation, pulmonary artery catheters
Mental status changes/seizures	TTP, ehrlichiosis
Renal failure	TTP, dengue, HIT, DIC
Cardiac failure	HIT, drug induced, pulmonary artery catheter, heart valve hemolysis
Post-surgery	Dilutional, drug-induced, HIT
Pregnancy	HELLP syndrome, fatty liver of pregnancy, TTP/HUS
Acute liver failure	Splenic sequestration, HIT, drug induced, DIC

Abbreviations: DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver function tests, and low platelets; HIT, heparin induced thrombocytopenia; TTP, thrombotic thrombocytopenic purpura.

Table 3
Diagnostic clues to coagulation defects

Clinical setting	Differential diagnoses
Cardiac surgery	Factor V inhibitor, heparin excess or rebound, protamine excess, fibrinolysis
Sepsis syndrome	Isolated factor VII deficiency, DIC, vitamin K deficiency,
Recent use of quinine, 2nd or 3rd generation cephalosporin	Drug induced hemolysis/DIC syndrome
Post-surgery	Dilutional, DIC, thrombin inhibitors
Pregnancy	HELLP syndrome, fatty liver of pregnancy, vitamin K deficiency
Acute liver failure	Consumption, DIC, fibrinolysis, vitamin K deficiency (biliary obstruction)

Abbreviations: DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver function tests, and low platelets.

Massive transfusions

The massively transfused patient is defined as one who receives greater transfused blood than one blood volume in 24 hours or less [22]. A practical definition is receiving one blood volume in 2 hours or less. The most common settings for massive transfusion are trauma or gastrointestinal bleeding [23]. Management of blood products is outlined above. The use of a laboratory guided transfusion protocol has helped to reduce the mortality in patients requiring massive transfusions [24,25].

Box 4. Massive transfusions

The five basic tests of hemostasis

Hematocrit
Platelet count
Prothrombin time (PT-INR)
Activated partial thromboplastin time (aPTT)
Fibrinogen level

Management guidelines

Platelets <50–75,000/uL: give 1–2 units of apheresis (''single donor'') platelets or 6–8 units of whole blood derived (''random donor'') platelets
Fibrinogen <100–125 mg/dL: give 10 units of cryoprecipitate
Hematocrit <30%: give red cells
PT-INR >1.6–2.0 and aPTT abnormal: give 2–4 units of FFP

Coagulation defects are common in the massively transfused patients [26]. These can be caused by dilution of the plasma by massive fluid resuscitation or by red cell transfusions. Packed red cell units contain little plasma (about 25–50 mL/unit), and massive replacement of blood volume with packed red blood cells can lead to a dilutional coagulopathy. Patients may also develop a coagulopathy caused by their underlying medical or surgical conditions. Prolonged hypotension may be associated with severe ongoing coagulopathy even after normotension is restored.

It is not possible to predict the degree of coagulopathy from the amount of blood transfused, and formulaic replacement of factors—give so many units of plasma for so many units of red cells transfused—should be avoided [27]. Some patients may receive 20 units of packed red cells and still have good hemostatic functions; others may have florid coagulopathies caused by injuries before the first unit of blood is given. Therefore, monitoring the patient's coagulation status during massive transfusions is crucial.

Correcting coagulation defects before procedures

A common question is, at what platelet count is it safe to perform invasive procedures such as central venous line placement? Procedures such as central venous line placement are frequently done successfully on patients with anticoagulation [28–31]. One study found the risk was not related to the degree of hemostatic defects [32]. In this study, the risk of hemorrhage was higher when inexperienced operators attempted line placement. For urgent line placement, experience of the operator is more important than to waiting for transfusion therapy [32]. In a non-urgent situation, increasing the platelet count to 30–50,000/uL may be a reasonable goal, a necessary procedure should not be delayed by trying to achieve an arbitrary platelet count target.

Coagulation defects

Disseminated Intravascular Coagulation

DIC is the clinical manifestation of inappropriate thrombin activation [33–36]. The activation of thrombin leads to (1) fibrinogen conversion to fibrin, (2) platelet activation and consumption, (3) activation of factors V and VIII, (4) protein C activation (and degradation of factors Va and VIIIa), (5) endothelial cell activation, and (6) fibrinolysis.

Patients with DIC can present in one of four patterns [33,35].

Asymptomatic. Patients can present with laboratory evidence of DIC but no bleeding or thrombosis. This is often seen in patients with sepsis or cancer. However, with further progression of the underlying disease, these patients can rapidly become symptomatic.

Bleeding. The bleeding is caused by combinations of factor depletion, platelet dysfunction, thrombocytopenia, and excessive fibrinolysis [33]. These patients may present with diffuse bleeding from multiple sites.

Thrombosis. Despite the general activation of the coagulation process, thrombosis is unusual in most patients with acute DIC. The exceptions include cancer patients, trauma patients, and certain obstetrical patients. Most often the thrombosis is venous, but arterial thrombosis and non-bacterial thrombotic endocarditis have been reported [37].

Purpura fulminans. This severe form of DIC is described in more detail later.

The best way to treat DIC is to treat the underlying cause [33,34,36,38]. However, one must replace factors if depletion occurs and bleeding ensues. Management should be guided by following the basic tests of coagulation.

Heparin therapy is reserved for the patient who has thrombosis as a component of their DIC [34,39,40]. Reliance on the aPTT to follow heparin therapy may lead to over- or under-treatment of patients; heparin levels in these patients should be followed [41,42].

Purpura fulminans

DIC in association with symmetrical limb ecchymosis and necrosis of the skin is seen in two situations [43]. Primary purpura fulminans is most often seen after a viral infection [44]. In these patients the purpura fulminans starts with a painful red area on an extremity that rapidly progresses to a black ischemic area. In many patients acquired deficiency of protein S is found [43,45,46].

Secondary purpura fulminans is most often associated with meningococcemial infections but can be seen in any patient with overwhelming infection [47–49]. Post-splenectomy sepsis syndrome patients are also at risk [50]. Patients present with signs of sepsis and the skin lesions often involve the extremities and may lead to amputations.

The best therapy for purpura fulminans has not been established. Primary purpura fulminans, especially those with post-varicella autoimmune protein S deficiency, has responded to plasma infusion titrated to keep the protein S level more than 25% [43]. Intravenous immune globulin has also been reported to help decrease the anti-protein S antibodies. Heparin therapy may control the DIC and limit the extent of necrosis [51]. The starting dose in these patients is 5–8 units/kg/hr [34].

Patients with secondary purpura fulminans have been treated with plasma drips, plasmapheresis, and continuous plasma ultrafiltration [51–54]. Heparin therapy alone has not been shown to improve survival [55]. Much attention has been given to replacement of natural anticoagulants such as protein C and antithrombin as therapy for purpura fulminans, but unfortunately randomized trials using antithrombin have shown mostly negative results [43,46,56–58]. Trials using either zymogen protein C concentrates or recombinant activated protein C (rAPC) have shown more promise in controlling the coagulopathy of purpura

Box 5. Treatment of purpura fulminans

Drotrecogin 24mcg/kg/hr for 96 hours
Blood product support to maintain
PT-INR <2
aPTT <1.8 times normal (drotrecogin will raise aPTT by 5–7 seconds)
Platelets >50,000/uL
Consider continuous veno-venohemofiltration

fulminans and improving outcomes in sepsis [52,59–61]. Although bleeding is a concern with use of protein C, most complications occur in patients with platelet counts under 30,000/uL or in those who have meningitis [62]. If rAPC is used, other parameters of coagulation should be carefully monitored (Box 5).

Drug induced hemolytic-disseminated intravascular coagulation syndromes

A severe variant of drug-induced immune complex hemolysis associated with DIC has been recognized, most commonly to cephalosporins or to quinidine. Rare patients who receive certain second and third generation cephalosporins, especially cefotetan and ceftriaxone, have developed this syndrome [63–67]. The clinical syndrome of severe Coombs positive hemolysis, hypotension, and DIC starts 7 to 10 days after receiving the drug. Often the patient has only received the antibiotic for surgical prophylaxis, is believed to have sepsis, and is reexposed to the offending cephalosporin, resulting in worsening of the clinical picture. The outcome is often fatal because of massive hemolysis and thrombosis [66,68–70]. Quinine is associated with a unique syndrome of drug-induced DIC [71–74]. Approximately 24–96 hours after quinine exposure, the patient becomes acutely ill with nausea and vomiting. The patient then develops a microangiopathic hemolytic anemia, DIC, and renal failure. Some patients, besides having antiplatelet antibodies, also have antibodies binding to red cells and neutrophils that may lead to the more severe syndrome. Despite therapy, patients with quinine-induced thrombotic thrombocytopenic purpura (TTP) have a high incidence of chronic renal failure.

Evidence for treatment of the drug induced hemolytic-DIC syndrome is anecdotal. Patients have responded to aggressive therapy including plasma exchange, dialysis, and prednisone. Early recognition of the hemolytic anemia, and the suspicion it is drug related is important for early diagnosis so that the incriminating drug can be discontinued.

Vitamin K deficiency

Vitamin K is crucial in the synthesis of coagulation factors II, VII, IX, and X. Patients obtain vitamin K from food sources and from of intestinal flora. Despite

being a fat soluble vitamin, body stores of vitamin K are low and the daily requirement is 40–80 mcg/d.

Vitamin K deficiency can present dramatically [75]. Once the body stores of vitamin K are depleted, production of the vitamin K-dependent proteins ceases and the INR will increase rapidly to high levels. The diagnosis is suspected when there is a history of prolonged antibiotic use, biliary obstruction, or pre-existing malnourishment [75–77].

Treatment (and a diagnostic test of vitamin K deficiency) is by replacement of vitamin K. Most patients will respond rapidly to 10 mg orally. For a more rapid (4–6 hours) and reliable response, 5–10 mg may be given over 30–60 minutes intravenously. Alternatively, plasma can be used for the patient with life or limb threatening bleeding and marked elevation of the PT-INR. At least 4 units of plasma may be needed until the administered vitamin K takes effect.

Thrombocytopenia and platelet dysfunction

Heparin induced thrombocytopenia

Heparin induced thrombocytopenia (HIT) occurs because of the formation of antibodies directed against the complex of heparin that is bound to platelet factor IV [78–84]. Despite the presence of thrombocytopenia, thrombosis and not bleeding is the major clinical problem. The frequency of HIT is 1%–5% when unfractionated heparin is used but <1% with low molecular weight heparin [85]. HIT should be suspected when there is a sudden onset of thrombocytopenia with either at least a 50% drop in the platelet count or the platelet count falling to <100,000/uL in a patient receiving heparin in *any* form. HIT usually occurs 4 days after starting heparin but may occur suddenly in patients with recent (<3 months) exposure [86–88]. An often overlooked presentation of HIT is recurrent thrombosis in a patient receiving heparin who has a platelet count which has fallen but is still in the "normal range" [89].

The diagnosis of HIT can be challenging in the critical care patient who has multiple reasons for being thrombocytopenic. In this situation a positive laboratory assay for HIT may be helpful. Two general types of HIT assays exist. The first type is the functional assays. These use patient plasma, normal platelets, and varying concentrations of heparin. Heparin-dependent platelet activation at therapeutic heparin concentrations constitutes a positive assay. Functional assays include the 14-C serotonin release assay, lumiaggregometry, and heparin-dependent platelet aggregation assays. These tests are technically demanding (particularly the serotonin–release and lumiaggregometry, which use washed donor platelets) but if performed carefully are both sensitive and specific for HIT [86,90]. One caveat is that early in HIT, functional assays can be negative because of low antibody titers, but then turn positive 24 hours later as the antibody titer increases. Retesting if the initial assay is negative or indeterminate is rec-

ommended in this clinical context. The second type of HIT assays is the platelet calcium/heparin antibody ELISA assays. These detect the presumptively pathogenic HIT antibodies. Unfortunately, the PF4/heparin antibody response is polyclonal, and only a subset of these antibodies cause clinical HIT. Therefore, the ELISAs tend to be too sensitive in many patient populations at risk for HIT. For example, 25%–50% of reoperative cardiac patients will be positive [91,92] for PF4/heparin antibodies when tested by ELISA, and most of these will be false positives. HIT can also be caused by other types of antibodies and some of the HIT ELISAs can be negative in up to 20% of HIT cases because of non antiplatelet calcium antibodies [93,94]. These problems make HIT ELISA assays difficult to rely upon for definitive clinical diagnosis of HIT.

The first step in therapy of HIT consists of stopping all heparin. Low molecular weight heparins cross-react with the HIT antibodies and, therefore, these agents are also contraindicated [86]. Institution of warfarin therapy alone has been associated with an increased risk of thromboses [86] and patients with acute HIT should only be warfarinized after complete recovery of the platelet count, and then only under coverage with another antithrombotic agent. For immediate therapy of HIT patients, three new antithrombotic agents are available [95,96] (Box 6).

Argatroban is a synthetic thrombin inhibitor [97–99] with a short half-life of 40–50 minutes. Dosing is 2 mcg/kg/min with the infusion adjusted to keep the aPTT 1.5–3 times normal. One advantage of argatroban is that it is not renally excreted and no dose adjustment is necessary in renal failure [100]. These characteristics make it the most useful agent for patients in the critical care unit. However, argatroban must be used with caution in patients with severe liver disease with an initial dose of 0.5 mcg/kg/min and titrated upward [99]. Also it is prudent to start at 1 mcg/kg/min in patients with multiorgan system failure [101]. Argatroban (like all thrombin inhibitors) prolongs the PT-INR making transition to warfarin therapy difficult as the PT-INR will be prolonged on argatroban alone, and further prolongation will not reliably reflect the degree of anticoagulation with warfarin. If available, a chromogenic factor X assay can be used to adjust warfarin therapy [102]. Chromogenic factor X levels of 0.2 to 0.3 normally correspond to therapeutic PT-INRs of 2.0–3.0 once the argatroban is stopped. If a chromogenic factor X is not available, and if the patient is on a drip of 2 mcg/kg/min or less, simply aim for a PT-INR of >4.0 as indicative that therapeutic anticoagulation on warfarin has been achieved before stopping the argatroban. Unfortunately there is no agent that can reverse argatroban.

Lepirudin, another direct inhibitor of thrombin, is also monitored by using the commonly available aPTT. The half-life of lepirudin is short, but the drug accumulates in renal insufficiency with the half-life increasing to >50 hours. There is no antidote for lepirudin. Patients with even slight renal insufficiency (creatinine >1.5) must have their lepirudin doses adjusted to avoid overanticoagulation [103]. Up to 80% of patients receiving long-term lepirudin therapy will develop antibodies [104,105]. These antibodies reduce the metabolism of hirudin and *increase* the therapeutic effect of lepirudin. Patients on

Box 6. Treatment of heparin induced thrombocytopenia

Argatroban

Therapy: 2 mcg/kg/min infusion with dose adjustments to keep aPTT 1.5–3 times normal. Decrease dose to 0.5 mcg/kg/min in severe liver disease

Hirudin

Therapy: bolus of 0.4 mg/kg followed by 0.15 mg/kg/hr to maintain an aPTT of 1.5–3.0 times normal

For creatine of 1.6–2.0 mg/dL: bolus of 0.2 mg/kg followed by a 50% reduction in infusion rate

For creatine of 2.0–2.5: bolus of 0.2 mg/kg followed by a 75% reduction in infusion rate

For creatine of 2.6–6.0:bolus of 0.2 mg/kg followed by a 90% reduction in infusion rate

For creatine of greater than 6.0 mg/mL: bolus of 0.1 mg/kg on alternate days only when the aPTT is less than 1.5 times normal and no infusion

Fondaparinux

Prophylaxis: 2.5 mg/d

Therapy: <50 kg body weight: 5 mg/d

50–100 kg body weight: 7.5 mg/d

>100 kg body weight: 10 mg/d

Use with caution and monitor by anti-Xa levels in renal insufficiency (Note: monitoring is not often readily available outside of specialized centers)

Data from: Laposata M, Green D, Van Cott EM, et al. The clinical use and laboratory monitoring of low-molecular-weight heparin, danaparoid, hirudin and related compounds, and argatroban. Arch Pathol Lab Med 1998;122:799–807. Hirsh J, Warkentin TE, Raschke R, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. Chest 1998;114:(Suppl 5):10S. Kondo LM, Wittkowsky AK, Wiggins BS. Argatroban for prevention and treatment of thromboembolism in heparin-induced thrombocytopenia. Ann Pharmacother 2001;35:440–51. Cook GC, Zumla A, editors. Manson's tropical diseases. Philadelphia: W.B. Saunders; 2004.

long-term (>6 days) lepirudin therapy should still continue to be monitored to avoid over-anticoagulation.

The new anti-Xa inhibitor fondaparinux does not cross-react with HIT antibodies and may be useful for prophylaxis in HIT and as clinical experience accumulates for therapy [106].

As mentioned above, initiation of warfarin alone has been associated with limb gangrene and should not be started as the sole antithrombotic agent in HIT. In patients receiving specific antithrombin therapy, warfarin can be started with small doses (2–5 mg). These often malnourished patients tend to have a dramatic response to warfarin therapy and excessive anticoagulation can easily occur. One should overlap warfarin and parental therapy by 2–3 days as there is evidence patients may do worse with shorter specific antithrombin therapy [99].

Patients with HIT but without evidence of thrombosis are at a high risk of thrombosis (53% in one study) [107] and should be considered for antithrombotic therapy [108,109]. Patients with HIT should also be carefully screened for any thrombosis including obtaining lower extremity dopplers. It is unknown whether prophylactic doses are necessary or if therapeutic doses of anticoagulants are needed for thrombosis prevention in patients with HIT but no thrombosis. Also, the duration of such therapy is controversial. One approach is to give prophylactic doses of antithrombotic agents until the platelet count has returned to normal [109]. In post surgical patients, prolonged prophylaxis for up to 6 weeks may be of benefit.

Thrombotic thrombocytopenic purpura

TTP should be suspected when a patient presents with the combination of thrombocytopenia and microangiopathic hemolytic anemia (schistocytes and signs of hemolysis) [110,111]. Critical care patients with TTP most often present with intractable seizures, strokes, or sequela of renal insufficiency. Many patients who present to the critical care unit with TTP will have been misdiagnosed as having sepsis, lupus cerebritis, or vasculitis.

Evidence is strong that many patients with the classic form of TTP have an inhibitor against an enzyme that is responsible for cleaving newly synthesized von Willebrand factor (vWF) [112]. vWF is synthesized as an ultra-large multimer that can spontaneously aggregate platelets. The enzyme, ADAMTS13, is a protease which cleaves vWF into the smaller forms that normally circulate and do not spontaneously aggregate platelets [113,114]. Presumably in TTP, inhibition of ADAMTS13 leads to circulation of ultra-large vWF multimers with resulting spontaneous platelet aggregation leading to the clinical syndrome of TTP. However, other factors also appear to be involved in the pathogenesis of TTP, because many patients with classic TTP have normal activity of ADAMTS13, and reduced levels of the protease are also found in other diseases [115–117].

There is currently no single definitive laboratory test for TTP. Rather the diagnosis of TTP is based on the clinical presentation [110,111]. Patients uniformly will have a microangiopathic hemolytic anemia with the presence of

schistocytes on the peripheral smear. Renal insufficiency rather than frank renal failure is the most common renal manifestation. Thrombocytopenia may range from mild decreases in platelet number to platelets being undetectable. The lactate dehydrogenase (LDH) is often extremely elevated and is a prognostic factor in TTP [118]. Although measurement of ADAMTS13 activity level of immense research and perhaps prognostic interest, for the reasons discussed above, it is not of diagnostic value.

Untreated TTP is rapidly fatal. Mortality in the pre-plasma exchange era ranges from 95% to 100%. Today plasma exchange therapy is the cornerstone of TTP treatment and has reduced mortality to <20% [111,119–121].

Glucocorticosteroid therapy (ie, 60–120 mg of prednisone) is routinely given to patients presumed to have TTP. This should be continued until the patient has fully recovered and perhaps longer, given the presumed autoimmune nature of the disease and the high relapse rates. Plasma infusion is beneficial [112]. Plasma exchange has been shown to be superior to simple plasma infusion in therapy of TTP [119]. This may be because of the ability of plasma exchange to give very large volumes of fresh frozen plasma, and removal of inhibitory antibodies. In patients who cannot be immediately exchanged, plasma infusions should be started at a dose of 1 unit every 4 hours. Patients with all but the mildest cases of TTP should receive 1.5 plasma volume exchange each day for at least 5 days [111]. Plasma exchange should be continued daily until the LDH has normalized. Frequency of exchange should be taped starting with every-other day exchange. If the platelet count falls or LDH level rises, daily exchange should be reinstated [110]. Since the platelet count can be affected by a variety of external influences, the LDH level tends to be the most reliable marker of disease activity [122].

Therapy related thrombotic microangiopathies

TTP/hemolytic uremic syndrome (HUS)-like syndromes or more precisely, thrombotic microangiopathies, can complicate a variety of therapies [123]. Thrombotic microangiopathies can be associated with medications such as cyclosporin, FK506, mitomycin, and ticlopidine. Thrombotic microangiopathy occurs within days after cyclosporine/FK506 is started, with the appearance of a falling platelet count, falling hematocrit, and rising serum LDH level [124]. Some cases have been fatal but often the thrombotic microangiopathy resolves when the cyclosporine dose is decreased or changed to another agent.

Thrombotic microangiopathies are most commonly seen when the antineoplastic agent mitomycin C is used, and with an incidence of 10% when a dose of more than 60 mg is used [125]. Anecdotal reports state that treatment with staphylococcal A columns may be useful for this condition [126]. These columns work by absorbing immune complexes, but their mechanism in mitomycin thrombotic microangiopathies is unknown. Since advanced cancer itself can be associated with a TTP-like syndrome, it may be caused by the cancer and not the cancer treatment.

Thrombotic microangiopathies can complicate both autologous and allogenic bone marrow transplants [127–129]. The incidence ranges widely depending on the criteria used to diagnosis the thrombotic microangiopathy, but it is in the range of 15% for allogeneic and 5% for autologous bone marrow transplants. Several types of thrombotic microangiopathies are recognized in the bone marrow transplantation setting [128,129]. The first is the "multi-organ fulminant" type, which occurs early (20–60 days post transplant), has multi-organ system involvement, and is often fatal. This type has also been associated with severe cytomegalo virus (CMV) infection. A second type is similar to the cyclosporin/FK 506 HUS type described above. A third "conditioning" thrombotic microangiopathy has been described, which occurs 6 months or more after total body irradiation, and is associated with primary renal involvement. Finally, patients with systemic CMV infections may present with a thrombotic microangiopathy related to vascular infection with CMV. The etiology of bone marrow transplant (BMT)-related thrombotic microangiopathy appears to be different from that of "classic" TTP. Alterations of ADAMTS13 have not been found in BMT-related TTP; rather therapy-related vascular damage has been implicated as the likely etiological [130]. Optimal therapy of BMT-related thrombotic microangiopathies is uncertain. Patients should have their cyclosporine or FK506 doses decreased. Although plasma exchange is often tried, patients with fulminant or conditioning-related thrombotic microangiopathies do not normally respond [131,132].

Pregnancy thrombocytopenic syndromes

One should consider three syndromes in the critically ill pregnant woman who presents with thrombocytopenia. These are the HELLP (Hemolysis, Elevated Liver tests, Low Platelets) syndrome, fatty liver of pregnancy, and TTP (Table 4) [133,134].

Table 4
Pregnancy related diseases

Finding	HELLP	TTP/HUS	AFLP
Hypertension	Always present	Sometimes present	Sometimes present
Proteinuria	Always present	Sometimes present	Sometimes present
Thrombocytopenia	Always	Always	Always
LDH elevation	Present	Marked	Present
Fibrinogen	Normal to low	Normal	Normal to very low
Schistocytes	Present	Present	Absent
Liver tests	Elevated	Normal	Elevated
Ammonia	Normal	Normal	Elevated
Glucose	Normal	Normal	Low

Abbreviations: AFLP, acute fatty liver of pregnancy; HELLP, hemolysis, elevated liver tests, and low platelets; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic uremia syndrome.
Data from: Egerman RS, Sibai BM. Imitators of preeclampsia and eclampsia. Clin Obstet Gynecol 1999;42:551–62. Esplin MS, Branch DW. Diagnosis and management of thrombotic microangiopathies during pregnancy. Clin Obstet Gynecol 1999;42:360–7.

The acronym HELLP describes a variant of pre-eclampsia [135]. Classically, HELLP syndrome occurs after 28 weeks of gestation in a patent suffering from pre-eclampsia but can occur as early as 22 weeks in patients with antiphospholipid antibody syndrome [136–138]. The pre-eclampsia need not be severe. The first sign is a decrease in the platelet count followed by abnormal liver function tests. Signs of hemolysis are present with abundant schistocytes on the smear and a high LDH. HELLP can progress to liver failure and deaths have also been reported due to hepatic rupture. Unlike TTP, fetal involvement is present in the HELLP syndrome, and fetal thrombocytopenia has been reported in 30% of cases [139]. In severe cases, elevated D-dimers consistent with DIC are also found. Delivery of the child will most often result in cessation of the HELLP syndrome but refractory cases will require dexamethasone and plasma exchange [140]. Patients should be closely observed for 1–2 days after delivery as the hematologic picture can transiently worsen before improving [132].

Fatty liver of pregnancy also occurs late in pregnancy and is only associated with pre-eclampsia in 50% of cases [133,141,142]. Patients first present with non-specific symptoms of nausea and vomiting but can progress to fulminant liver failure. Patients develop thrombocytopenia early in the course but in the later stages can develop DIC and very low fibrinogen levels. Mortality rates without therapy can be a high as 90%. Low glucose and high ammonia levels can help distinguish fatty liver from other pregnancy complications [134]. Treatment consists of prompt delivery of the child and aggressive blood product support.

TTP can occur anytime during pregnancy often leading to diagnostic confusion caused by the overlap symptoms between TTP and HELLP syndrome [134]. There does appear to be a unique presentation of TTP that occurs in the second trimester at 20–22 weeks [143]. The fetus is uninvolved with no evidence of infarction or thrombocytopenia if the mother survives. The pregnancy appears to promote the TTP since the TTP will resolve with termination of the pregnancy and can recur with the next pregnancy [144]. Therapy includes termination of the pregnancy or attempting to support the patient with plasma exchange until delivery. Many patients will have relapses with future pregnancies so this information must be weighed in planning future pregnancies. An unusual complication of pregnancy is a HUS-type syndrome seen up to 28 weeks post-partum. This form of HUS is severe, and permanent renal failure often results despite aggressive therapy [144].

Sepsis

Thrombocytopenia is a frequent finding in patients with sepsis syndrome [145–147]. Classically this has been ascribed to DIC or immune destruction. One mechanism receiving increasing attention is cytokine-driven hemophagocytosis of platelets [148–150]. Patients with hemophagocytosis had higher rates of multiple organ system failure and higher mortality rates. Inflammatory cytokines, especially monocyte-colony stimulating factor, are thought to be responsible for inducing the hemophagocytosis [146,151].

Thrombocytopenia may be a diagnostic clue to infection with unusual organisms. Three members of the Ehrlichia family of have been reported to cause infections in humans [152]. They are transmitted by ticks and the diseases that they produce are similar. Most patients have a febrile illness with high fevers, headaches and myalgias [152,153]. Patients may have central nervous system signs and marked elevation of the serum levels of liver enzymes. Rarely patients may present with a toxic shock-like syndrome [154]. Although many cases are mild, severe disease is common and the case fatality rate is 2%–5% [153]. The typical hematologic picture is leukopenia (1300–4000/uL) and mild thrombocytopenia (30–60,000/uL). In many patients the buffy coat reveals the organisms bundled in a 2–5 *u*m morula in the cytoplasm of the granulocytes or monocytes. Consideration of ehrlichiosis is important because highly specific therapy is doxycycline, which is a drug not routinely used for therapy of sepsis syndrome.

Hantavirus pulmonary syndrome (HPS) was described in 1993. Patients suffer a flu-like prodrome and then rapidly develop a noncardiac pulmonary edema resulting in profound respiratory failure [155,156]. Ventilatory support is required in 75% of cases and the mortality is approximately 50%. The peripheral smear can provide a powerful diagnostic predictor of hantavirus infection [156,157]. In a recent study, the triad of thrombocytopenia, increased and left-shifted white cell count, and more than 10% circulating immunoblasts, identified all cases of HPS and was seen in only 2.6% non-HPS [156]. Marked hemoconcentration is also present in hantavirus infection caused by capillary leak syndrome, with the hematocrit reaching as high as 68%.

Viral hemorrhagic fevers are a diverse group of viral infections including Lassa fever, Rift Valley fever, Ebola, and dengue, that can result in massive bleeding [158–161] (Table 5). The clinical pattern is a febrile illness that proceeds over a few days to shock and diffuse gastrointestinal and mucosal bleeding, with signs of thrombocytopenia and in some cases DIC. Most viral hemorrhagic fevers are associated with leukopenia and hemoconcentration. Therapy is aggressive supportive care of the patients and replacement of coagulation factors. Precautions should be taken to prevent nosocomial spread given the propensity of many of these infections to spread to health care workers [162].

Catastrophic antiphospholipid antibody syndrome

Rarely, patients with antiphospholipid antibody syndrome can present with fulminant multiorgan system failure [163–165]. Catastrophic antiphospholipid antibody syndrome (CAPS) is caused by widespread microthrombi in multiple vascular fields. These patients will develop renal failure, encephalopathy, adult respiratory distress syndrome (often with pulmonary hemorrhage), cardiac failure, dramatic livedo reticularis, and worsening thrombocytopenia [166]. Many of these patients have pre-existing autoimmune disorders and high titer-anticardiolipin antibodies. It appears that the best therapy for these patients is aggressive immunosuppression with plasmapheresis then (perhaps) IV cyclo-

Table 5
Viral hemorrhagic fevers

Arenaviridae	Bunyaviridae	Filoviridae	Flaviviridae
Diseases			
Lassa fever, new world arenaviruses	Crimean-Congo hemorrhagic virus (CCHF), Rift Valley fever, hemorrhagic fever with renal syndrome (HFRS)	Ebola, Marburg Viruses	Dengue, Yellow Fever
Distribution			
West Africa (Lassa), South America (rare California) (New world)	Africa, central Asia, eastern Europe, Middle East (CCHF), Africa, Middle East (Rift), Asia, Balkans, Europe (HFRS)	Africa	Widespread (Dengue), Africa, Tropical Americans (Yellow)
Vector			
Rodents	ticks (CCHF), mosquitoes (Rift Valley), rodents (HFRS)	?	Mosquitoes
Incubation			
5–16 days	1–6 days (CHHF), 2 weeks to 2 months (HFRS)	2–21 days	3–15 days
Therapy			
Ribavirin	Ribavirin		
Unique clinical Features			
pharyngitis, late deafness (Lassa); neurological involvement - seizures (New world)	retinitis, hepatitis (Rift Valley), prominent bleeding with DIC, jaundice (CCHF); renal disease (CCHF)	Maculopapular rash, high mortality	liver involvement (Yellow)

Data from: Cook GC, Zumla A, editors. Mansion's tropical disease. Philadelphia: W.B. Saunders; 2004. Hunter GW, Strickland TG, Magill AJ, Kersey R, editors. Hunter's tropical medicine and emerging infectious diseases. 8th Edition. Philadelphia: W.B. Saunders; 2004.

phosphamide monthly. Early recognition of this syndrome can lead to quick therapy and resolution of multiorgan system failure.

Cardiopulmonary bypass

Cardiopulmonary bypass (CPB) results in very complex and still poorly defined defects in all aspects of hemostasis, including platelets, coagulation factors, and fibrinolysis [167–173]. If the patient is still in the operating suite and starts to have microvascular bleeding, the platelet count, PT-INR, aPTT, and fibrinogen should all be checked and defects corrected appropriately. In particular, patients who have had multiple transfusions of cell-saver blood or of packed red cells may

have dilutional coagulation defects that need to be treated. In the bleeding patient still on bypass, in whom obvious coagulation defects (thrombocytopenia, prolonged PT-INR, low fibrinogen) have been corrected by appropriate transfusion of platelets, plasma or cryoprecipitate, an infusion of desmopressin (ddAVP) may be indicated. Once off pump, full heparin reversal by protamine should be assured. Given the platelet defect induced by CPB, if the patient is still bleeding after ddAVP, transfusion of platelets is indicated. PT-INR and PTT should also be verified as being in the normal range. If bleeding still persists despite this one dose of rVIIa is a logical next step [174].

If bleeding occurs in the postoperative setting, coagulation tests should be obtained and surgical hemostasis assured. Again, attention should be paid to the PT-INR, PTT, and fibrinogen levels. Often patients will respond to empiric transfusions of platelets. In the immediate postoperative state, a heparin level, if available, or a thrombin time should be checked to insure the patient is not experiencing "heparin rebound," particularly if the PTT is prolonged.

Uremia

Before the advent of dialysis, bleeding was a common late complication of uremia [175–178]. Life threatening bleeding is uncommon but dialysis patients have a high incidence of gastrointestinal bleeding and subdural hematomas. The defect in uremia appears to be a platelet function defect [177,179].

Uremic patients who are bleeding should have a PT-aPTT and platelet count performed. Patients with uremia are prone to vitamin K deficiency so assessment of the PT is important. The half-life of both unfractionated and low molecular weight heparin is increased in renal failure. Patients usually receive a bolus of heparin with dialysis and rare patients will have a persistently prolonged anticoagulant effect. Low molecular weight heparins are cleared in the kidneys and if the dose is not adjusted, levels can greatly increase above therapeutic levels. Bleeding times are prolonged in renal disease. Unfortunately there is little correlation between prolongation of the bleeding time and actual bleeding, especially following procedures.

Multiple treatment options exist for uremic bleeding (Box 7). Patients who are severely uremic and are bleeding may respond to aggressive dialysis [180]. Cryoprecipitate is not consistently effective [180,181].

Desmopressin is effective, and the bleeding time shortens for at least 4 hours after infusion [182]. Patients can exhibit tachyphylaxis with desmopressin; this agent is not useful for repeated dosing.

For chronic bleeding, an infusion of conjugated estrogens will shorten the bleeding time. The dose is 0.6 mg/kg/d intravenously for 5 days. The onset of action takes up to 1 day but lasts for 2 weeks after the series of infusions [183].

Raising the hematocrit above 30% will shorten the bleeding time in some situations. This can be done either by transfusion or chronically with the use of erythropoietin [184]. For purposes of hemostasis, the target hematocrit with the

Box 7. Therapy for uremic bleeding

Acute

Aggressive dialysis
Desmopressin (DDAVP) 0.3 mcg/kg IV
Cryoprecipitate 10 units

Long term

Conjugated estrogen 0.6 mg/kg for 5 days
Erythropoietin or darbepoietin to increase hematocrit >30%

use of erythropoietin should be 27%–30% Uremic patients who present with severe bleeding may benefit from transfusion of red cells.

Drug-induced thrombocytopenia

In patients with a possible drug-induced thrombocytopenia, the standard therapy is to stop the suspect drug [185,186]. In a patient receiving multiple essential drugs this is often impractical [3,6]. One approach is to stop any drug started in the past 7 days that is strongly associated with thrombocytopenia [187] (Box 8). Substituting sucralfate or a proton-pump inhibitor for H_2-blockers is another option. Unfortunately, critically ill patients are often receiving many therapeutic agents known (rarely) to cause thrombocytopenia but essential for treatment. In this situation, one option is to support the patient with platelet transfusions until the agent can be discontinued.

Immune globulin, corticosteroids, or intravenous anti-D have been suggested as useful in drug-related thrombocytopenia. However, since most patients with this type of drug-related thrombocytopenia recover rapidly when the agent is cleared from the body, such therapies are not normally necessary and should be avoided in the interest of sparing the patient possible associated side effects and toxicities.

Drug-induced platelet dysfunction

Sophisticated testing of platelet function has revealed that acquired abnormalities are extremely common but the clinical significance, if any, of these abnormalities is controversial [188]. Many of these proposed abnormalities are only reflected in an increased bleeding time, a test of uncertain clinical value [189].

Multiple drugs have been shown to inhibit platelet function, but clinical bleeding has only been associated with a few. Aspirin has been shown to be associated with increased risk of bleeding in clinical trials [188]. Ketorolac has

Box 8. Common drugs implicated in thrombocytopenia

Anti GP IIb/IIIa agents

Abciximab
Eptifibatide
Tirofiban

Antimicrobial

Amphotericin B
Ethambutol
Rifampin
Trimethoprim-sulfamethoxzole
Vancomycin

Cardiovascular Agents

Amiodarone
Amirone
Captopril
Digoxin
Methyldopa
Procainamide
Quinidine

H2-blockers

Cimetidine
Ranitidine

Acetaminophen
Carbazepine
Gold
Heparin
Hydrochlorothiazide
Non-steroidal antiinflammatory agents
Phenytoin
Quinine
Valproic Acid

Data from: DeLoughery T. Drug induced immune hematological disease. Immunol Allergy Clin N Am 1998;18:829–41. George JN, Raskob GE, Shah SR, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 1998;129:886–90. Greinacher A, Eichler P, Lubenow N, et al. Drug-induced and drug-dependent immune thrombocytopenias. Rev Clin Exp Hematol 2001;5:166–200.

also been associated with significant clinical bleeding [190–192]. This is especially true with combined use of ketorolac and heparin or in patients with other bleeding defects such as von Willebrand disease.

Hydroxyethyl starch (HES) is frequently associated with acquired hemostatic defects [193]. Bleeding may occur, especially with prolonged use of this agent or with the use of more than 1.5 L/d. Decreased levels of both vWF and factor VIII are seen, and many patients will have an acquired type 2 von Willebrand disease (vWD) defect with selective loss of the higher weight vWF multimers, which are particularly important in mediating platelet adhesion [194–201]. Levels of vWF will normalize gradually after the HES is stopped. Patients who have received HES and bleed should have a vWD panel drawn. If abnormal, factor replacement should be used to correct bleeding. Daily monitoring and therapy may be necessary for 3–5 days until the defects have fully corrected.

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