



ICT 2023

28th International
Congress on Thrombosis

Sepsis, Thrombosis and organ dysfunction

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20'



Declaration of Conflict Of Interest

- I have no potential conflict of interest to report
X
- I have the following potential conflict(s) of interest to report

Sepsis- Definition

- The term has a very ancient origin, from the Greek 'ζεψις', meaning decomposition of organic material. Its first mention is even found in Homer.
- It was not until the germ theory of the 19th century, however, that sepsis was defined as a systemic pathological state of an infectious nature, the precise pathophysiological mechanisms of which are still a matter of debate.
- Sepsis can be understood as a continuum of a severe and potentially progressively worsening pathway that starts with an infection and leads to an inflammatory response, septic shock and finally to multiple organ dysfunction syndrome (MODS) and death.

Sepsis and septic shock are the most common cause of Disseminated Intravascular Coagulation

- Main clinical presentation: Hemorrhage
- Thrombocytopenia, prolonged PT and aPTT, hypofibrinogenemia, increased D-dimer
- Digital ischemia (microthrombi): 5-10%

Type of infection in DIC

- **Bacterial (gram-negative sepsis, gram-positive sepsis)**
- Rickettsiosis (rocky mountain spotted fever, scrub typhus)
- Viral (HIV, CMV, HSV, rotavirus, influenza, varicella-zoster virus, Ebola, dengue, COVID19)
- Fungal (histoplasmosis, candida sepsis, aspergillosis, Candida auris)
- Parasitic (malaria, leishmaniasis, babesiosis)

From Sepsis to Disseminated Intravascular Coagulation

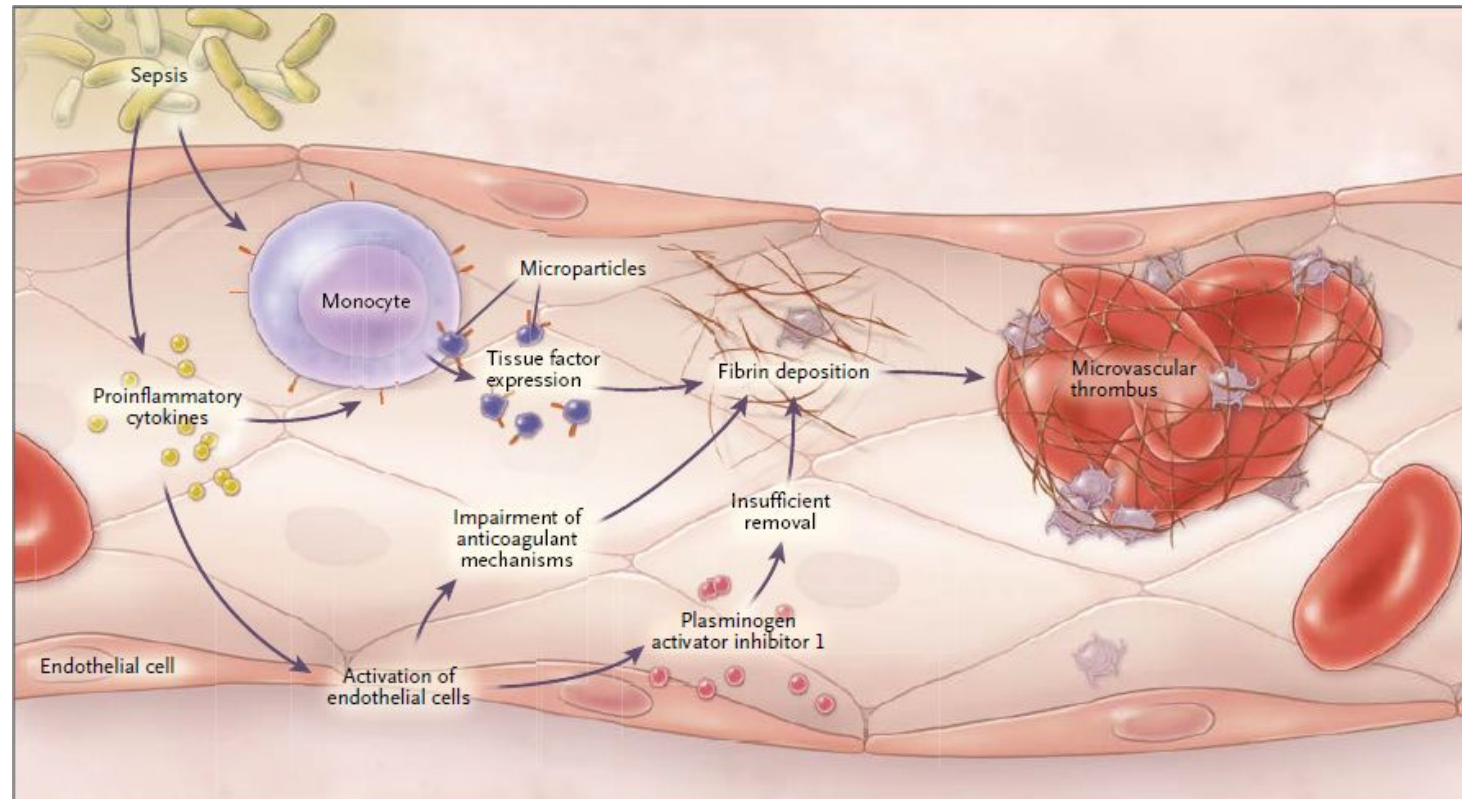
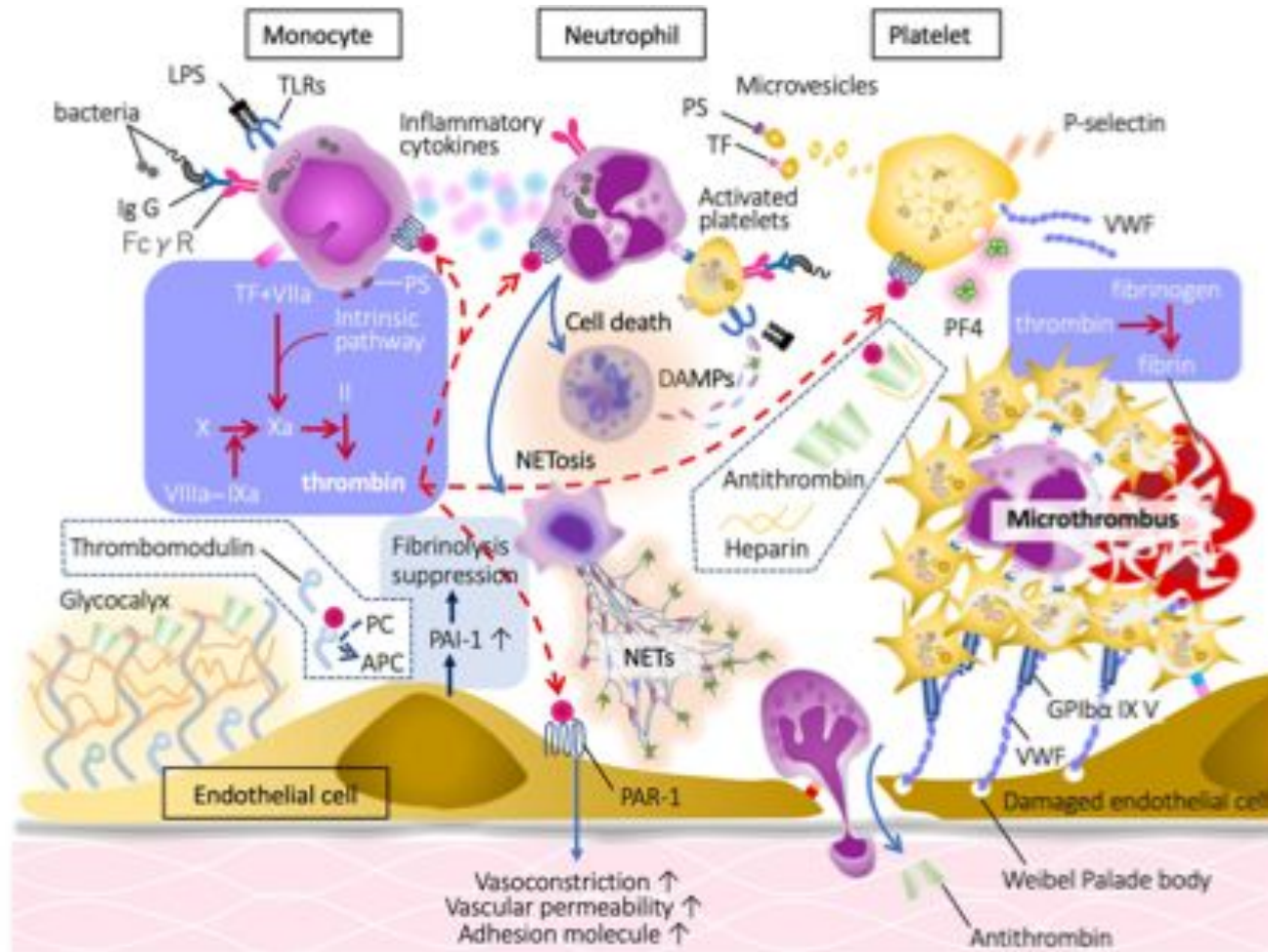


Figure 2. Pathogenesis of Disseminated Intravascular Coagulation in Sepsis.

Through the generation of proinflammatory cytokines and the activation of monocytes, bacteria cause the up-regulation of tissue factor as well as the release of microparticles expressing tissue factor, thus leading to the activation of coagulation. Proinflammatory cytokines also cause the activation of endothelial cells, a process that impairs anticoagulant mechanisms and down-regulates fibrinolysis by generating increased amounts of plasminogen activator inhibitor.

Pathophysiology of sepsis-associated coagulation disorder.



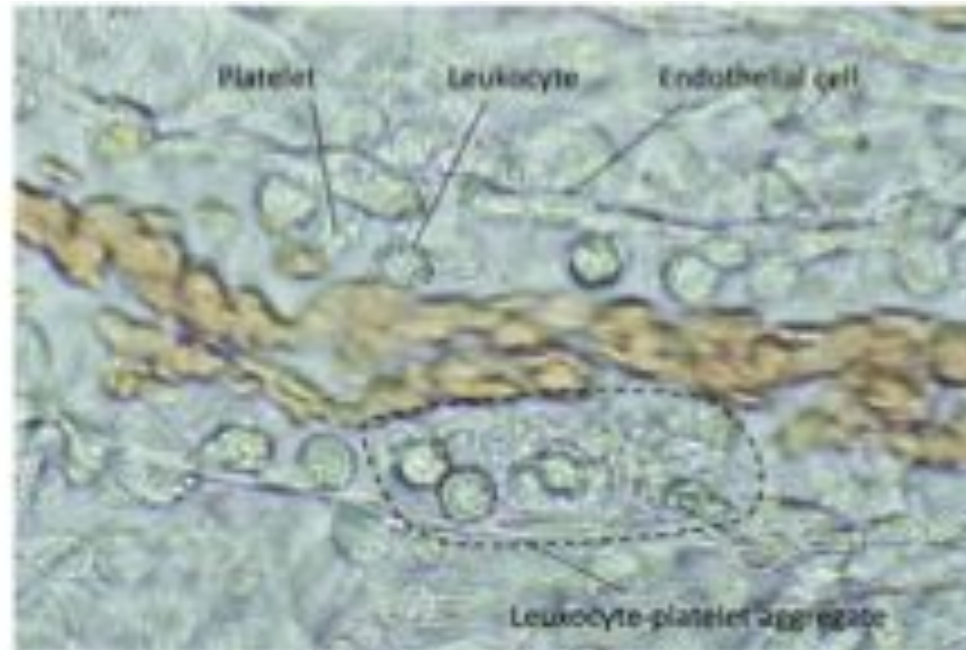
Monocytes, neutrophils and platelets express receptors such as Toll-like receptors (TLRs) Fcγ receptor (FcγR) and Protease Activated Receptor (PAR)-1 and induce procoagulant response in these cells.

Granulocytes release extracellular traps (NETs)

Endothelial cells become swollen and lose their antithrombotic properties.

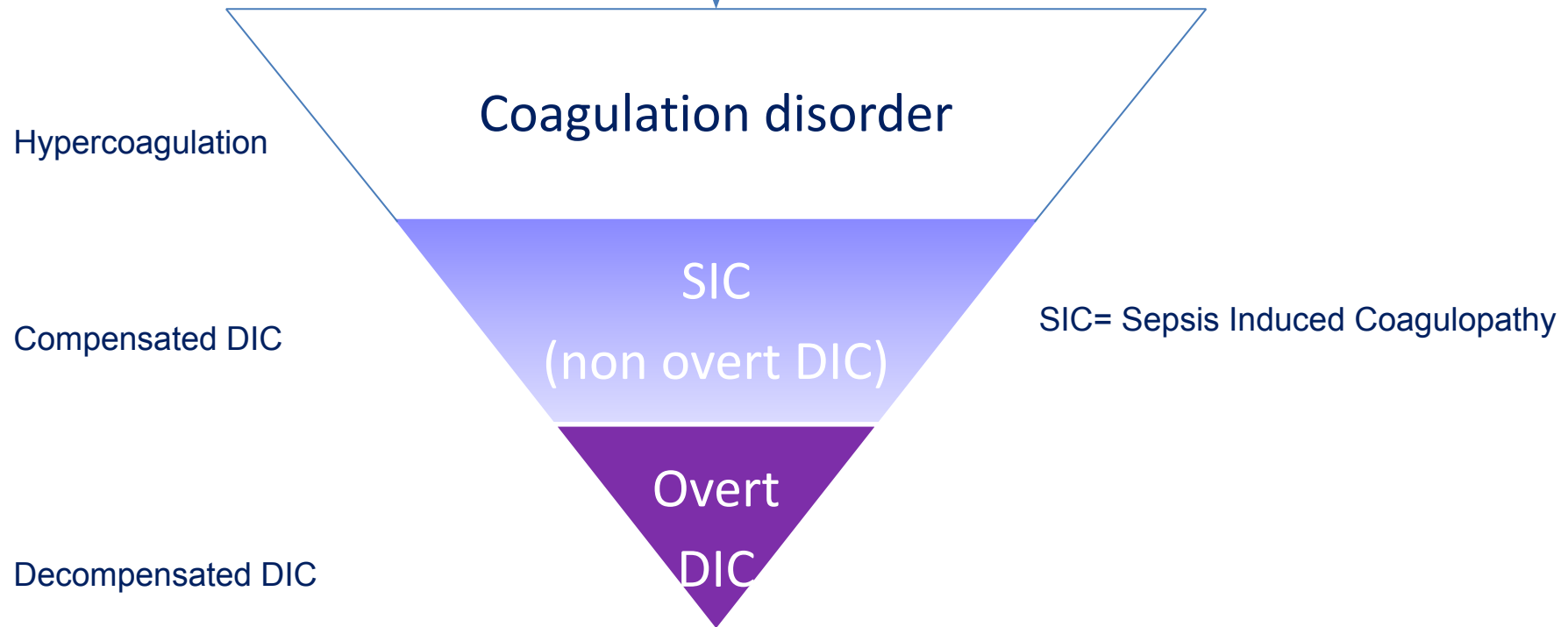
Platelets surface becomes thrombogenic, and release of vWF that promote platelet aggregation.

Microthrombosis in the mesenteric microcirculation in sepsis model of rat after lipopolysaccharide injection.



Round leukocytes adhered to swelled endothelial cells and some transmigrated to the extravascular space. Aggregated platelets stick to the leukocytes and endothelium and form leukocyte-platelet aggregation. Along with these changes, the blood flow gradually decreased... ORGAN DAMAGE

Sepsis



Disseminated Intravascular Coagulation (DIC) belongs to Thrombotic MicroAngiopathy (TMA) family

TMA definition

A histopathological condition characterized by thrombotic occlusion at the level of the microcirculation (arterioles and capillaries), with consequent organ dysfunction. The composition of the microthrombi is variable (in some cases fibrin prevails, in others the platelets, more often the composition is mixed).

Hemolytic
anemia-thrombocytopenia-schistocytes
Plus organ damage

Suspicion of
TMA

Thrombotic MicroAngiopathies (TMA)

TTP Thrombotic thrombocytopenic purpura

HUS Hemolytic-uremic syndrome

HELLP syndrome (pregnancy-related hemolysis, increased liver enzyme levels, thrombocytopenia)

CAPS Catastrophic antiphospholipid syndrome

DIC Disseminated Intravascular Coagulation

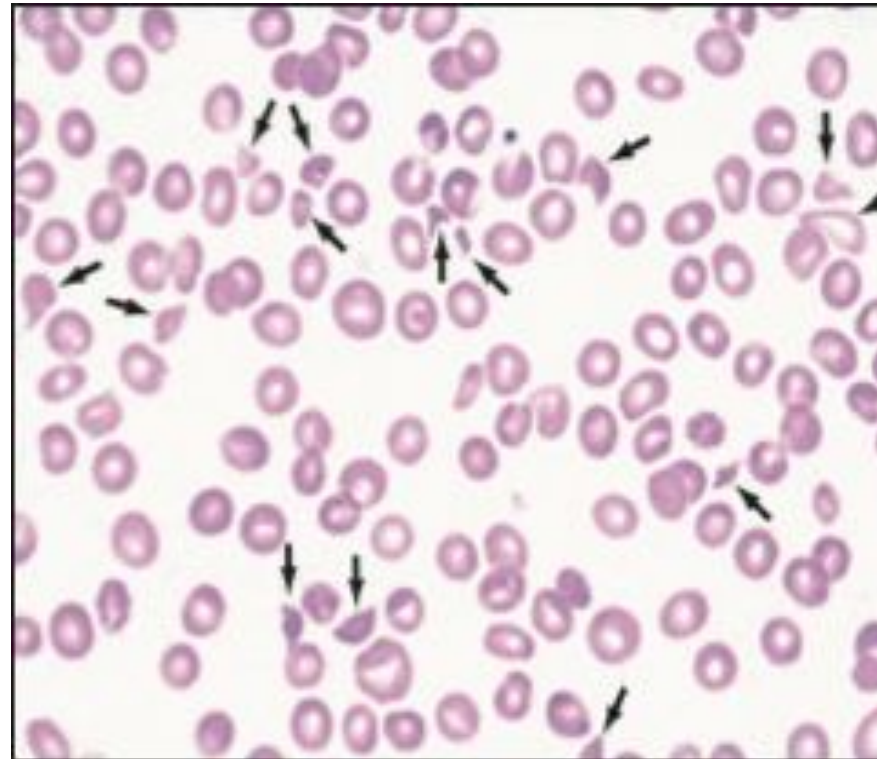
HIT Heparin-Induced Thrombocytopenia

Clinical and laboratory findings in thrombotic microangiopathies (TMA)

	Previous history of	Thrombosis of	Fibrinogen level	Haemolytic anemia	Schistocytes	Thrombocytopenia	Antibodies
CAPS	PAPS/ SLE	Small/ large vessels	Normal/ high	+/-	+	+	aPL
TTP HUS	Malignancy	Small vessels	Normal/ high	+	++	++	Anti- ADAMTS13
HELLP	Pregnancy	Small vessels	Normal/ high	+	+/-	++	-
DIC	Infection/ malignancy	Small vessels	Low	+/-	+/-	++	-
HIT	Heparin exposure	Large/ small vessels	Normal	-	+/-	++	Anti- HeparinPF4

Main characteristic; red cells fragmentation

Schistocytes



Schistocytes on peripheral blood smear. Up to three schistocytes per high-power field is normal. Arrows show more than 10 schistocytes per high-power field.

Diagnostic Scoring System for DIC¹

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

If yes, proceed with this algorithm

If no, do not use this algorithm

Order global coagulation tests (prothrombin time, platelet count, fibrinogen, fibrin-related marker)

Score the test results as follows:

Platelet count: 50,000 to 100,000 per mm³, 1 point; <50,000 per mm³, 2 points

Elevated fibrin-related marker (e.g., D-dimer, fibrin degradation products): no increase, 0 points; moderate increase, 2 points; strong increase, 3 points

Prolonged prothrombin time: <3 sec, 0 points; ≥3 sec but <6 sec, 1 point; ≥6 sec, 2 points

Fibrinogen level: ≥1 g per liter, 0 points; <1 g per liter, 1 point

Calculate the score as follows:

≥5 points: compatible with overt DIC; repeat scoring daily

<5 points: suggestive of nonovert DIC; repeat scoring within next 1 to 2 days

* Data are adapted from Toh and Hoots²¹ on the basis of the scoring system developed by the International Society on Thrombosis and Hemostasis.

¹Toh CH, Hoots WK; SSC on Disseminated Intravascular Coagulation scoring system of the ISTH. J Thromb Haemost. 2007 Mar;5(3):604-6.

Hemorrhagic bullae in a patient with DIC



Disseminated Intravascular Coagulation-Treatment

- Management: early treatment of the septic status
- Use of activated protein C (Ranieri VM, NEJM 2012), antithrombin (Afshari A, Cochrane 2008), TFPI (Abraham E, JAMA 2003) and thrombomodulin (Japan) showed no reduction in the rate of death and increased the bleeding episodes.
- Non evidence –based treatments are: platelet transfusion (if less than 50.000), fresh-frozen plasma (to maintain PT ratio less than 1.5), fibrinogen (to maintain fibrinogen level to more than 1.5 g/L)
- Heparin use is controversial
- Use of antifibrinolytic agents is contraindicated

Case Presentation

- A 77-years-old man whose medical history included treated hypertension and hypercholesterolemia, previous heavy alcohol intake and mild cognitive impairment was admitted to ICU after a proctosigmoidectomy procedure for fecal peritonitis. He was undergoing mechanical ventilation and was in septic shock.
- He received fluid resuscitation, noradrenergic, antibiotics and LMWH 5000U twice daily. He required sedation with propofol infusion.
- The patient's nurse noted slight bleeding from his abdominal wound and from around his venous and arterial catheters.
- Laboratory tests from that morning include low hemoglobin level (8.9g/dL), low platelet count (54.000 mmc), prolonged PT (1.6), prolonged aPTT (52 sec.), D-dimer 1100 and a fibrinogen level of 1.7g/L, 6 schistocytes in blood smear > 10.

Score calculation: Platelets 1, prolonged PT (4 sec.) 1 point , D-dimer 2 points = total 4 points i.e. NON OVERT DIC

Participants' response to the Delphi method

Which of the following strategies would you use in this patient?

Cease heparin and transfuse packed red cells, platelets, cryoprecipitate, and fresh-frozen plasma or prothrombin complex concentrate.

11%

Cease heparin and transfuse cryoprecipitate and fresh-frozen plasma or prothrombin complex concentrate.

33%

Cease heparin, transfuse platelets, administer an antifibrinolytic agent (e.g., epsilon-aminocaproic acid or tranexamic acid).

9%

Cease heparin and repeat laboratory tests in 8 to 12 hours.

45%

Poll closed February 26, 2014

(4272 total Responses)

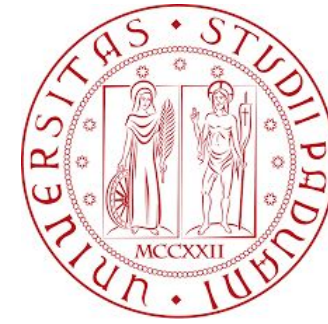
Answer (I)

- Thrombocytopenia with mildly abnormal coagulation tests, schistocytes in the blood smear, increased D-dimer.
- Slight bleeding from the surgical wound.
- Septic shock
- Conclusion: Early compensated DIC, repeat lab test every 12 h.

Answer (II)

- The management of DIC should be focused primarily on treatment of the underlying cause (sepsis).
- Experts suggest replacement of coagulation proteins and platelets in patients who are bleeding.
- Platelets to maintain platelet count of more than 50.000 mmc.
- Fresh frozen plasma to maintain PT and aPTT of less than 1.5 times the normal control time.
- Fibrinogen should be kept at a level of more than 1.5g/L.
- Antifibrinolytic agents are contraindicated.

Special thanks to my collaborators



University of Padua
Established in 1222

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[Anatomical Theatre of Padua](#)



[Aula Magna \(Great Hall\)](#)

Critical Care Medicine

Presentation of Case

A 77-year-old man whose medical history includes treated hypertension and hypercholesterolemia, previous heavy alcohol intake, and mild cognitive impairment is admitted to the intensive care unit (ICU) of a university hospital from the operating room after a Hartmann's procedure performed for fecal peritonitis due to a perforated sigmoid colon. On arrival in the ICU, he was undergoing mechanical ventilation and was in septic shock. He received fluid resuscitation with Hartmann's solution and 5% human albumin solution. His blood pressure was supported with a norepinephrine infusion. In addition to intravenous antibiotics, his treatment included subcutaneous unfractionated heparin (5000 U twice daily). On the day after admission to the ICU, his blood pressure is stable and supported by a reducing dose of norepinephrine. Analgesia is being provided by a continuous morphine infusion. However, despite adequate analgesia, he intermittently requires sedation in the form of low-dose propofol by infusion to tolerate the endotracheal tube. (In the previous installment of this case, there were 3894 votes on strategies for treating delirium and the use of sedation. A total of 15% of respondents favored the use intermittent intravenous lorazepam, 28% favored continuous intravenous infusion of propofol to facilitate daily cessation of sedation, 36% favored an intravenous infusion of an α 2-adrenoceptor agonist such as dexmedetomidine with daily cessation, and 18% favored no sedation.)

The patient's nurse notes slight bleeding from his abdominal wound and from around his arterial and central venous catheters. Laboratory test results from that morning include normal liver-function tests, a hemoglobin level of 8.9 g per deciliter, a platelet count of 54,000 per cubic millimeter, an international normalized ratio of 1.6, an activated partial-thromboplastin time (APTT) of 52 seconds, and a fibrinogen level of 1.7 g per liter.

Question

How would you assess and manage his bleeding? Polling and commenting are now closed. The editors' recommendations appear below.

Hartmann's procedure: proctosigmoidectomy

Critical Care Medicine

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soluzione isotonica cristalloide

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Cease heparin and repeat laboratory tests in 8 to 12 hours.



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9%

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45%

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Answer

The laboratory test results indicate the patient has thrombocytopenia with mildly abnormal results on coagulation testing. In addition, there is slight bleeding from the surgical wound and skin-puncture sites. However, the patient does not have worsening shock, which would be suggestive of substantial intraabdominal bleeding.

Coagulation abnormalities are very common in critically ill patients, and more than one cause may be present. Our patient has septic shock, which is the most common cause of disseminated intravascular coagulation (DIC). The laboratory results are consistent with early or low-grade DIC with a reduced platelet count and prolonged prothrombin time. Additional information should be sought from a blood smear to confirm thrombocytopenia, as well as checking levels of d-dimer and fibrin degradation products.

DIC is a clinicopathological diagnosis with the prerequisite that the patient must have an underlying disorder known to be associated with DIC. The scoring system of the International Society on Thrombosis and Hemostasis can be used to confirm that the laboratory diagnostic criteria have been met.¹ The management of DIC should be focused primarily on treatment of the underlying cause. General guidelines for the management of coagulopathy and bleeding are based mainly on expert opinion and suggest replacement of coagulation proteins and platelets in patients who are bleeding. Guidelines suggest platelet transfusion to maintain a platelet level of more than 50,000 per cubic millimeter and fresh-frozen plasma to maintain a prothrombin time and APTT of less than 1.5 times the normal control time, as well as a source of fibrinogen to maintain a fibrinogen level of more than 1.5 g per liter. Antifibrinolytic agents are contraindicated in the management of DIC, since the fibrinolytic system is needed to ensure dissolution of widespread fibrin during the recovery phase. Other possible contributing causes should be considered. The prolonged prothrombin time could be due to liver dysfunction associated with his previous alcohol intake, and the low platelet count could be due to hypersplenism associated with portal hypertension, but the normal results on other liver testing and the lack of history of cirrhosis are against this possibility.

The patient has received unfractionated heparin, and if he has previously been exposed to heparin, a diagnosis of heparin-induced thrombocytopenia (HIT) is a possibility. If he has not previously been exposed to heparin, then HIT is very unlikely after only 1 day of exposure. Screening tests for HIT, such as detection of platelet factor 4 antibodies on enzyme-linked immunosorbent assay, are now widely available, but false positives may occur in up to 80% of patients, and a confirmatory test (e.g., serotonin release assay) should be performed if the screening test is positive.²

Since it is likely that our patient has DIC associated with only minor bleeding, it is reasonable to simply withhold heparin and repeat the laboratory tests in 8 to 12 hours, or sooner if there is evidence of increased bleeding.

Thrombotic microangiopathies (TMA)

In 1924, Moschcowitz described a 16-year-old girl with weakness, pallor, purpura, and hemiparesis who died after 14 days with cardiac failure. Autopsy revealed hyaline thrombi in terminal arterioles and capillaries throughout most organs, including the kidneys. This report was the first description of TMA, presumably TTP, also called ADAMTS13 deficiency–mediated TMA.

In 1982, unusually large multimers of von Willebrand factor were observed in patients with chronic, relapsing (hereditary) TTP. This finding led to the discovery of a von Willebrand factor–cleaving protease that was subsequently characterized as ADAMTS13.

ADAMTS13 cleaves von Willebrand factor multimers that are secreted from vascular endothelial cells. ADAMTS13 deficiency results in unusually large von Willebrand factor multimers and the risk of platelet thrombi in small vessels with high shear rates.

Classification of TMA

Hereditary: Mainly in children

Mutations in:

ADAMTS 13

Complement

Methylmalonic acid, homocysteine

diacylglycerol kinase

Acquired: Mainly in children

**ST-HUS Shiga toxin–mediated
(previous infection)**

Acquired: Mainly in adults

TTP (Antibodies to ADAMTS 13)

DIC (sepsis)

HIT (heparin)

HELLP (pregnancy)

CAPS (often previous infection)

TTP: thrombotic thrombocytopenic purpura;

DIC: Disseminated Intravascular Coagulation;

HIT: Heparin Induced Thrombocytopenia

HELLP: hemolysis, elevated liver enzymes, and low platelets.