

SEED Coagulation

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Coagulation emergencies – understanding why turnaround times are vital

Introduction

The haemostatic system is a highly regulated, fine-tuned interaction of multiple processes involving the blood vessel wall – principally the endothelium, platelets and the non-cellular blood constituents. When this balance is disturbed, patients may demonstrate signs and symptoms of either pathological thrombosis or bleeding. The laboratory has a crucial role in a) identifying the nature of the underlying haemostatic defect, and b) monitoring the response to any treatment intervention.

Why are turnaround times vital?

Depending on the underlying cause, the situation may deteriorate rapidly into a life-threatening condition that requires urgent clinical intervention. As these patients are inherently unstable, it is vital that coagulation tests are analysed and reported back to the requesting clinician within the shortest possible turnaround time (TAT).

One of the most common coagulation emergencies facing a clinician is a patient who is bleeding excessively for a reason that is as yet unexplained. An instinctive reaction would be to administer blood to a bleeding patient, but in certain cases this could worsen rather than improve the situation. In order to determine whether blood will indeed be beneficial to the patient, and moreover which component of blood (plasma or platelets) would help, one would have to know the nature of the haemostatic defect. Is primary haemostasis (platelets) or secondary haemostasis (plasma factors) impaired, or both? While history and clinical presentation may suggest one or the other, rapid laboratory confirmation is essential for initiating the appropriate treatment

as a matter of urgency. Furthermore, the longer the delay between blood sampling and the availability of results, the greater the likelihood that the results may no longer be a true reflection of the patient's current clinical status and may lead therefore to less than optimal intervention, with potentially harmful consequences for the patient.

The clinical spectrum of coagulation emergencies

Since haemostatic balance is achieved by the interplay of a wide range of inputs, the spectrum of clinical conditions that can be associated with coagulation abnormalities, and consequently progress to a life-threatening situation, is very wide. This can range from uncontrollable bleeding to thrombosis of a single major blood vessel, such as occurs in stroke or myocardial infarction. While the latter patients may benefit from urgent intervention to open up the blocked vessels by means of thrombolytic drugs to restore blood flow to vital organs, and in doing so minimise the extent of permanent tissue damage. This text focuses on those conditions that depend on laboratory investigations for both diagnosis and monitoring the response to treatment. The latter include systemic thrombotic disorders, such as thrombotic thrombocytopenic purpura (TTP), as well as various inherited and acquired bleeding diatheses.

Patients with inherited bleeding abnormalities, although relatively uncommon in the general population, are frequent visitors to hospitals' accident and emergency departments. However, as haemophilia and Von Willebrand's disease have been previously described in separate SEED editions, this edition focuses only on acquired conditions.

Disseminated intravascular coagulopathy (DIC)

DIC is a clinical syndrome comprised of both thrombosis and bleeding due to unregulated release of thrombin into the general circulation. This leads to widespread micro-vascular micro-clot formation, which in turn causes tissue ischaemia that results in organ damage. The body responds to this by switching on the fibrinolytic system. Plasmin is generated, which breaks down fibrin in an attempt to maintain vascular patency. However, fibrinogen is also degraded in this process and results in bleeding that is exacerbated by concomitantly decreasing levels of clotting factors due to consumption during unregulated clot formation. DIC is not itself a disease, but rather a manifestation of some other underlying disorder. Conditions associated with DIC are shown in Tab. 1.

a) Severe infection	Bacterial septicaemia Haemorrhagic viral infections (e.g. Ebola, Dengue Fever) Severe malaria
b) Obstetric complications	Placental abruption Retained products of conception/dead foetus Amniotic fluid embolism Eclampsia/preeclampsia
c) Major trauma	Any serious tissue damage Fat embolism Head injury
d) Malignancy	Leukaemias (especially acute promyelocytic leukaemia) Solid tumours
e) Severe immunological/allergic/toxic reaction	Incompatible blood transfusion Snake or spider bites Ingestion of plant toxins
f) Vascular disorders	Any vascular malformation

Tab. 1 Conditions associated with DIC

Depending on the underlying cause, the clinical spectrum can range from subclinical laboratory abnormalities to multi-organ failure, haemodynamic instability, widespread bleeding and death. DIC is still widely perceived by clinicians to be primarily a bleeding disorder. This is unfortunate as by the time bleeding is overt, organ damage caused by thrombosis is already fairly advanced. As the signs and symptoms of early stage DIC are subtle, and DIC can progress very rapidly, the diagnostic focus has shifted. Any patient with any condition known to cause DIC and any suspicion of deterioration, be it a slight change in level of responsiveness, a minor drop in oxygen saturation, a reduction in

urine output, or oozing at venepuncture sites (already a later stage sign), requires urgent laboratory investigation for a possible underlying DIC.

Multiple scoring systems exist, but as a baseline one would measure platelet count, D-dimers, prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen. Patients with DIC have elevated D-dimers, thrombocytopenia (or at least a falling platelet count), prolonged clotting times and decreasing fibrinogen levels. Correction studies confirm that the prolonged PT and APTT are due to factor deficiencies. Further investigation by means of individual factor assays will confirm generalised consumption. The degree of prolongation of the PT and APTT depends on the degree to which clotting factor consumption is offset by the rate of synthesis. In turn, the rate at which the individual clotting factor assays become progressively abnormal depends on the half-life of each protein. In this regard, factor VII ($T_{1/2} \sim 5$ hours) is the first factor to become depleted while factor II is conserved the longest ($T_{1/2} \sim 65$ hours). Measuring antithrombin (also referred to as ATIII) is also helpful as this natural anticoagulant is consumed as the coagulopathy progresses. Low values are associated with poor prognosis.

Serial monitoring of the baseline tests mentioned above is vital as trends are often far more informative than single test results. Moreover, underlying diseases may predispose to more than one clinicopathological syndrome. For example, pregnancy complications are a commonly observed cause of DIC in clinical practice. Likewise, pregnancy is one of the commonest conditions associated with the acquired thrombotic microangiopathies, of which thrombotic thrombocytopenic purpura is most important because of the high risk of mortality. It is vital to discriminate between these two possibilities, as both can have similar presenting features, both can result in rapid deterioration and culminate in death, yet need to be treated differently. The laboratory plays a vital role in this regard. In TTP, the cardinal baseline laboratory abnormality is thrombocytopenia with or without moderately elevated D-dimers, but baseline coagulation tests are normal.

Managing DIC must centre on treating the underlying cause, which is easier said than done. Where bleeding is uncontrollable, blood product support may be required.

The general approach is to give only the components that are lacking and only as much as is required. The best way to judge whether the DIC is under control is to observe a drop in D-dimers. Improvement of other parameters (PT, APTT, fibrinogen, platelets, AT) could simply be a reflection of blood component replacement therapy.

Thrombotic microangiopathies

The thrombotic microangiopathies are a group of related disorders characterised by widespread small vessel occlusion. The hallmark features are thrombocytopenia, due to consumption as the thrombi are classically platelet-rich, and red cell fragmentation due to shredding of red cells as they pass through the obstructed microcirculation. As this mechanical haemolysis progresses, anaemia ensues – so-called microangiopathic haemolytic anaemia (MAHA). There are several causes of MAHA all of which have very similar clinical features while the underlying cause, and hence required treatment, may be significantly different. The conditions mentioned below have been highlighted not because they are common, but because they are associated with high mortality. The treatment differs significantly from DIC and needs to be implemented rapidly in order to be life-saving.

a) Thrombotic thrombocytopenic purpura (TTP)

Platelet-rich clots in the microvasculature occur due to the secretion of unusually large VWF multimers, which have an enhanced affinity for platelets. When they are secreted from the endothelial cells, these multimers are usually cleaved into smaller molecules by an enzyme called ADAMTS-13. If this enzyme is deficient (which can be familial or acquired) these ultra-large multimers adhere to the endothelium and initiate the formation of platelet aggregates. Acquired TTP is more common than the inherited form, and is known to be associated with HIV infection and pregnancy. The classical clinical features are shown in Tab. 2.

b) Haemolytic uremic syndrome (HUS)

Gastrointestinal infection with toxin-producing bacteria, most classically E.coli O157:H7, precedes the development of renal failure due to microthrombi formation because of toxin-induced damage to the kidney endothelium. Platelet consumption results in thrombocytopenia.

Thrombotic thrombocytopenic purpura	Haemolytic uremic syndrome
Thrombocytopenia	Thrombocytopenia
Microangiopathic haemolytic anaemia	Microangiopathic haemolytic anaemia
Renal failure	Prominent renal failure (usually follows an acute diarrhoeal illness)
Neurologic abnormalities	
Fever	

Tab. 2 Classic clinical features of TTP and HUS

c) HELLP Syndrome

This is a condition that occurs in pregnancy – haemolysis, elevated liver enzymes and low platelets – most commonly following preeclampsia. Preeclampsia is hypertension induced by pregnancy that develops after 20 weeks of gestation and is associated with proteinuria and, commonly, foetal growth retardation. The pathology is thought to be due to endothelial damage in the placenta, kidneys and other organs and can be fatal for both mother and foetus.

Clinically, these thrombotic microangiopathies, and DIC, may be very difficult to distinguish from one another. The first and most important step would be to perform the baseline clot-based coagulation screening tests mentioned previously, as these would be normal in the MAHA syndromes but deranged, or becoming progressively prolonged upon serial monitoring, in DIC. Thrombocytopenia is a common feature and all may have some degree of elevated D-dimers, although this is most pronounced, with progressive increments, in DIC. Pregnant patients are particularly challenging as all the conditions mentioned are possible. Delivery of the foetus will result in prompt resolution of symptoms in HELLP syndrome, but these will persist in cases of TTP/HUS. TTP/HUS in contrast requires urgent plasma exchange or plasma infusion. Its therapeutic benefit is based on the replacement of the missing ADAMTS-13 enzyme in the case of TTP and removal or dilution of the toxin in HUS.

Massive blood transfusion

Massive blood transfusion is defined as the replacement of 50% of total blood volume in 4 hours or total blood volume in 24 hours. In an adult total blood volume is about 70ml/kg and in a child about 80ml/kg. Any adult receiving 4 or more units of packed cells of blood in 4 hours will be at risk of developing a transfusion-associated coagulopathy, which will manifest as bleeding.

Massive transfusion is undertaken to replace rapid blood loss. The critical need is to restore oxygen-carrying capacity, and so packed red blood cells are transfused. The associated problem is that whole blood is replaced with packed red cells that are devoid of plasma or platelets. Consequently, thrombocytopenia and dilutional coagulopathy may ensue. This may be further exacerbated if the blood is not adequately warmed (often the case when rapid infusion is required) as clotting factors perform sub-optimally in hypothermic conditions. These patients may start oozing at surgical and venepuncture sites. The bleeding tendency in itself is not life threatening, but patients requiring massive transfusion are inherently unstable, hence any physiological aberration must be rectified as a matter of urgency. Massive transfusion recipients should be monitored during and immediately after the transfusion with baseline coagulation tests, i.e. PT, APTT, fibrinogen and platelets.

Some people have advocated the empirical infusion of plasma and platelet concentrates in a fixed ratio to the number of red cell units. There is however insufficient evidence that the use of fixed blood product replacement ratios of red cells to component therapy (FFP, platelets, cryoprecipitate) influences morbidity and mortality. Of course, the underlying problem that necessitated the transfusion in the first place (e.g. trauma, surgery, obstetric, gastrointestinal bleed etc.) as well as concomitant conditions, such as hypothermia and metabolic acidosis, will have an influence on the outcome. In this regard, the decision to infuse plasma, platelets or cryoprecipitate should be based on laboratory investigations. As the balance of haemostasis is precarious, and rapidly changeable in these patients, it is essential that laboratories provide rapid TATs for these coagulation tests.

Vitamin K antagonist overdose

Vitamin K antagonists such as warfarin are very commonly prescribed drugs, both as treatment of thrombosis and for long-term prophylaxis. Conditions that require anticoagulation are more common in the elderly. Elderly people are also more likely to be taking chronic medication for other ailments. Warfarin is a drug that has a very narrow therapeutic window as a variety of factors, including concomitant drug use, alter its biological activity. Consequently, laboratory monitoring is mandatory in order to minimise the risk of haemorrhagic complications or ongoing hypercoagulability. Despite extensive emphasis being placed on the importance of compliance with testing intervals, education of patients regarding possible interferences, and the need to come for testing should their medication (both prescribed and over-the-counter) change, bleeding due to excessive anticoagulation remains a common emergency department presentation. In most instances, the patient will inform the doctor that he or she is on warfarin. The management in this case will be to discontinue warfarin and oral or intravenous vitamin K or even plasma infusion (or prothrombin complex factor concentrate) in severe cases. The role of the laboratory is to establish the baseline INR and then to monitor its reversal back into the therapeutic range. Instinctively one might think that if a patient known to be on warfarin presents with a bleeding problem, then the cause is obvious and laboratory testing is not a priority. It should be remembered, however, that such patients are not immune to other problems so that it would be negligent to assume that warfarin overdose is the cause of bleeding without confirmation. Also, the treatment instituted for reversal would be influenced by the baseline INR result as it would be equally dangerous to completely normalise the INR. If this were to happen the patient would be at risk of thrombosis (e.g. stroke) which is why they are taking warfarin in the first case.

Accidental ingestion of warfarin tablets or rat poison (which contains very long-acting super-warfarins) by young children is also well documented. If the child was observed ingesting the drugs/poison, it would have been taken to the emergency department and the situation dealt with before warfarin

had exerted its anticoagulant effect. The cause of bleeding is therefore usually not obvious as it will take a couple of days post ingestion for bleeding to manifest. Here, the laboratory plays a vital role in ascertaining the cause of bleeding. A full baseline bleeding screen including platelet count, PT, APTT and fibrinogen is required. In the case of warfarin overdose, both the PT and APTT will be prolonged, and will normalise when correction studies are performed. The management would be vitamin K and plasma (or prothrombin complex concentrate if available) if bleeding is life threatening. In the case of super-warfarin poisoning, high dose vitamin K will be required for several months as the anticoagulant effects are very long-lasting. Frequent PT monitoring will be required.

Although bleeding may not appear life-threatening, one must remember that internal bleeding, especially a brain haemorrhage (both the elderly and children are prone to falling), may not be immediately obvious and must be excluded in every case.

Other bleeding emergencies

The inherited platelet function abnormalities (such as Bernard Soulier syndrome and Glanzmann thrombocytopenia) as well as acquired platelet disorders such as immune thrombocytopenic purpura may also present with severe bleeds requiring emergency management but are beyond the scope of this newsletter.

Take home message

- There is significant overlap in the clinical manifestations of the acquired coagulopathies – they occur in inherently unstable patients and carry a high risk of mortality. For treatment to be life-saving, it needs to be commenced early on.
- Differentiation of DIC from the MAHA syndromes is only possible with baseline coagulation tests. As a minimum, a platelet count, D-dimer, PT, APTT and fibrinogen need to be performed as a matter of urgency and subsequently monitored at regular intervals.
- Laboratory confirmation is vital as treatment is highly specific depending on the underlying pathophysiology.
- The laboratory must provide rapid TATs for these tests as the patients are unstable and require urgent intervention and monitoring of response to treatment.

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