# Hemostasis Testing in the Emergency Department: A Narrative Review

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Semin Thromb Hemost

## Abstract

Routine laboratory screening is typically performed at initial evaluation of the vast majority of presentations to the emergency department (ED). These laboratory results are crucial to the diagnostic process, as they may influence up to 70% of clinical decisions. However, despite the usefulness of biological assessments, many tests performed are inappropriate or of doubtful clinical relevance. This overutilization rate of laboratory testing in hospitals, which represents a significant medical–economic burden, ranges from 20 to 67%, with coagulation tests at the top of the list. While reviews frequently focus on nonintensive care units, there are few published assessments of emergency-specific interventions or guidelines/guidance to date. The aim of this review is to highlight current recommendations for hemostasis evaluation in the emergency setting with a specific analysis of common situations leading to ED admissions, such as suspected venous thrombosis or severe bleeding. We revisit the evidence related to the assessment of patient's hemostatic capacity based on comprehensive history taking and physical examination as well as best practice recommendations for blood sample collection to ensure the reliability of results. This review also includes an examination of various currently available point of care tests and a comprehensive discussion on indications, limitations, and interpretation of these tests.

**Keywords**

- emergency
- coagulopathy
- POCT
- direct oral anticoagulant
- viscoelastic testing
- APTT
- thrombosis
- appropriate prescription
- sustainability

**Issue Theme** Editorial Compilation—Part XVII; Guest Editors: Emmanuel J. Favaloro, PhD, FFSc (RCPA), Leonardo Pasalic, FRCPA, FRACP, PhD, Bingwen Eugene Fan, MBBS, MRCP, MMED, Giuseppe Lippi, MD


Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

**DOI** https://doi.org/10.1055/s-0044-1787661.
**ISSN** 0094-6176.

Routine laboratory screening is typically performed at initial evaluation of the vast majority of presentations to the emergency department (ED), except those with minor medical complaints. These laboratory results are crucial to the diagnostic process, as they may influence up to 70% of the clinical decisions, despite accounting for less than 5% of the hospital budget.[1] However, despite the usefulness of biological assessments, many tests performed are inappropriate or of doubtful clinical relevance.[2] The overutilization rates of laboratory testing in hospital, which represents a significant medical–economic and environmental burden, ranges from 20 to 67%, with coagulation tests at the top of the list.[3,4] Several effective initiatives have been launched to tackle this issue. These include, for example, the introduction of alerts that notify clinicians when a laboratory test is ordered while a recent test is already available for the same patient, and the "Choosing Wisely®" campaign on unnecessary tests and procedures in the health care system. The latter was launched in 2012 and involves 80 scientific societies, having since issued over 600 recommendations regarding tests and treatments commonly utilized within their respective fields, although they lack substantial supporting evidence.[5] Among these recommendations, some pertain to hemostasis tests performed in the ED such as "Do not measure the international normalized ratio (INR) in patients who are taking an anti-Xa inhibitor" or "Do not employ a specific direct oral anticoagulant (DOAC) reversal agent without identifying the DOAC and estimating its plasma concentration."

As for the "Choosing Wisely" campaign, multiple reviews have also assessed the published literature of interventions especially those led outside the ED in non-intensive care units (ICUs). However, there are few published assessments of emergency-specific interventions or guidelines/guidance to date.[6,7] Furthermore, there is critical need for swift interventions and prompt access to diagnostic information in the ED to manage critical patients, but also to reduce their length of stay. Traditional laboratory tests often face challenges such as prolonged turnaround times (TATs), which ideally should be under 60 minutes.[8] Point-of-care testing (POCT) emerges as a solution, providing immediate results at the patient's bedside, and streamlines the diagnostic process, reducing treatment delays, length of stay, and improving patient outcomes.[9] However, they suffer from several drawbacks, such as (i) significant variability that renders these tests noninterchangeable; (ii) lower analytical and/or clinical performances; (iii) higher cost than the high-throughput devices used in central laboratories; (iv) lack of appropriate training for staff performing the tests (with risk of errors in the analytical phase); (v) absence of systematic verification of preanalytical errors such as hemolysis, contamination from infusion fluids; (vi) necessity of predefined algorithms with decision-making thresholds; (vii) most of the POC devices increase the environmental burden as they are manufactured from unsustainable polymeric materials like thermoplastic and elastomers.[10–12] Taken together, POCT is one possibility to reduce the total TAT after interdisciplinary risk/benefit analysis and definition of an appropriate quality control program, regular staff training and documentation (e.g., by connecting devices to the Hospital or Laboratory information systems).[11]

The aim of this review is to highlight current recommendations for hemostasis evaluation in the emergency setting. We will review the approaches available to assess thrombotic and hemorrhagic risks in patients arriving at the ED. We will also conduct an in-depth analysis of proper blood collection techniques to ensure the reliability of test results. This study will include an examination of various currently available tests and a comprehensive discussion on the interpretation of abnormal findings.

## Hemostasis Test Indication

The main recommendation is against conducting systematic hemostasis tests on every patient who arrives at the ED.[13] Previous studies demonstrated the ineffectiveness of conventional coagulation tests in patients presenting with conditions such as chest pain,[14,15] as well as in assessing bleeding risks before surgery and anesthesia.[16] The relevance of hemostasis tests in the ED largely hinges on the clinical context. Some individual measures have proven beneficial. For instance, in cases where a patient undergoing low molecular weight heparin (LMWH) treatment presents with severe bleeding, promptly assessing anti-Xa activity is typically advisable to gauge the extent of anticoagulation, while INR assessment is recommended for patients on vitamin K antagonists (VKAs) therapy.[17,18] On occasion, a combination of tests may be warranted. For example, evaluating the activated partial thromboplastin time (aPTT), INR, thrombin time (TT), and anti-Xa activity collectively may be necessary to rule out the presence of significant anticoagulant levels in a patient suspected of anticoagulant drug intake without specific details.[19] Instead of relying solely on conducting laboratory tests to evaluate thrombotic or hemorrhagic risk, clinicians are encouraged to first assess this risk through patient comprehensive history taking and physical examination.

### Evaluation of Patients with Hemorrhagic Risk

The assessment of hemorrhagic risk in the ED will primarily be performed before an invasive procedure (preoperative evaluation) or when a hemorrhagic diathesis is suspected, for example, in patients presenting bleeding symptoms like hematuria or epistaxis. The initial stage of assessing the patient's hemostatic capacity in the ED should ideally rely on conducting a comprehensive patient interview. The clinician must seek for personal or family history of bleeding (for example: menorrhagia, epistaxis, or abnormal bleeding after surgery or trauma), which could raise a suspicion of an undiagnosed bleeding disorder. Certain bleeding disorders may remain undiagnosed until late adulthood, since routine coagulation tests might show normal results, and the bleeding episodes could be mistakenly considered insignificant. These bleeding disorders can be categorized into disorders of coagulation factors/hemostasis proteins (87%), platelet number and function (8%), and the fibrinolytic system (3%), with the remaining 2% identified as unclassifiable.[20] Bleeding

 

assessment tools proposed by societies such as the International Society on Thrombosis and Hemostasis (ISTH) for evaluation of bleeding disorders or questionnaires designed for preoperative hemostatic assessment are supports that can help physicians.[21,22] Medical comorbidities or active diseases such as liver failure, renal insufficiency, or sepsis can also have major repercussions on hemostasis, and must be considered by the clinician during patient management. Moreover, clinical examination can provide information on hemostasis capacity. Mucocutaneous bleeding or petechiae, for example, are easily identifiable signs of bleeding diathesis. Finally, special attention should be paid to medications that interfere with hemostasis, like nonsteroidal anti-inflammatory agents or antiplatelet drugs and anticoagulants as well as some dietary and nutriment effects.[23,24] Following this initial step, the issue of the hemostasis test utility emerges. The significance of performing standard hemostasis tests for critically ill or high-risk bleeding patients admitted to the ED remains unclear. Guidelines recommend performing those tests for patients with active hemorrhage or signs of bleeding, a known coagulopathy, a personal or familial bleeding history, those taking anticoagulants and for patients in critical situations (sepsis, preeclampsia, disseminated intravascular coagulation [DIC], etc.) or with liver failure.[13,25] These recommendations, however, are not widely followed. Nonadherence to guidelines may be due to ignorance regarding cost of the tests, uncertain diagnosis, defensive medicine practice, and the wide range of available tests.[26] These practices lead to increased hospital costs, hospital-acquired anemia, and unnecessary additional laboratory and radiological tests.[27]

## Evaluation of Patient Thrombosis Risk

### Venous Thromboembolism

Thrombotic risk assessment in the ED mainly focuses on patients with suspected venous thromboembolism (VTE) or those who require consideration for preventive anticoagulation. The exclusion of VTE involving ED assessment is seen in the context of an annual incidence of VTE in the Western world estimated to be approximately 0.75 to 2.69 per 1,000 individuals, with an increase over time and with age.[28] As with the hemorrhagic risk, the thrombotic risk is increased by clinical conditions and comorbidities such as obesity, pregnancy, or old age. The risk is also increased in some pathologies such as cancer, inflammatory disorders, infections and in some situations such as trauma, immobilization, surgery, or long travels. It is not recommended to test for thrombophilia in adults with VTE who have major transient risk factors. In the absence of predisposing factors, the clinician must seek a possible personal or family history of thrombosis which can raise suspicion of an undiagnosed inherited thrombophilic disorder such as Factor V Leiden, protein C, protein S, or antithrombin deficiencies, for example, but it is preferable not to test at the time of the VTE event due to interference with the results.[29,30] Normal results of thrombophilia screening can exclude these disorders, while abnormal levels should be confirmed by a repeated test. The presence of Factor V Leiden can be confirmed through a genetic analysis, which can be performed at any time. It is also essential to inquire about the patient's regular medication intake, with particular attention to medications like oral contraceptives, hormone replacement therapy, or cancer medications.

In emergency settings, primary thromboembolic events typically include lower limb thrombosis and pulmonary embolism (PE), with less common occurrences such as cerebral venous thrombosis (CVT), splanchnic venous thrombosis (SVT), and central retinal vein occlusion (CRVO) also being diagnosed.[31]

Deep vein thrombosis (DVT) typically manifests with nonspecific clinical symptoms such as acute pain, swelling, erythema in the lower extremities. Complications may include postthrombotic syndrome, PE and, in severe cases, death.[32] Main international evidence-based guidelines[33–35] recommend validated clinical decision rules for confirming or excluding DVT in both inpatients and outpatients. These rules integrate patient history and physical examination to categorize the pretest clinical probability of DVT into two (unlikely or likely) or three categories (low, intermediate, or high clinical).[36] Given these pretest probabilities, the Wells rule cannot be employed as a standalone test to confirm or exclude DVT; thus, it is commonly associated with D-dimer testing or ultrasonography.[37] D-dimers are soluble degradation products of fibrin resulting from plasmin-mediated degradation of cross-linked fibrin and can be considered biomarkers of in vivo activation of both coagulation and fibrinolysis. Depending on the assay employed, D-dimer tests may be classified as either high-sensitivity (>95%) and low-specificity (<40%), or moderate-sensitivity (80–94%) and high-specificity (up to 70%).[38] Highly sensitive D-dimer testing is recommended for populations with low (≤5%) or intermediate (~20%) clinical probability of lower extremity DVT, as this assay exhibits outstanding negative predictive value (NPV) in patients with low probability of DVT. The risk of false negatives is contingent upon the prevalence of the disease within the studied population, which is determined by the clinician's assessment of clinical probability. The threshold for classifying D-dimer results as negative has typically been established at a fixed level of 500 µg/L fibrinogen equivalent unit under the age of 50 to enhance sensitivity and NPV, with value increasing by 10 µg/L for each year of age after 50.[39] No further investigation is necessary if the D-dimer test yields negative results in patients where DVT is deemed unlikely. In case of positive results, performing proximal or whole-leg ultrasound is required to confirm the diagnosis. If DVT is not detected, the diagnosis will be excluded in populations with low clinical probability. For populations with intermediate probability, ultrasound should be repeated after 7 days to confirm the absence of DVT. In populations with high pretest probability (≥50%), D-dimer testing is not currently recommended. This approach is justified by Bayesian calculations, which suggest that patients who have a pretest probability >40% will have a posttest probability of >2% after a negative enzyme-linked immunosorbent assay (ELISA) D-dimer. To exclude the

 

presence of lower limb DVT in populations with high pretest probability, ultrasound examination is recommended as the initial step, with the possibility of repetition after 7 days, if necessary.

If a patient has suspected PE, main international guidelines propose the consideration of symptoms, clinical signs, and risk factors to classify the patient into one of three categories of pretest probability (low, moderate, and high probability) using a prospectively validated risk score (Wells rule and revised Geneva score).[35,40,41] The calculation of this pretest probability will help distinguish patient(s) with low and moderate probability, for whom a D-dimer assay is recommended before potential imaging, from patient(s) with high probability, for whom only imaging is required without D-dimer test to confirm or rule out the diagnosis of thromboembolic event. Currently, the measurement of D-dimer levels is recommended for patients with a low or intermediate clinical probability.[42] The proportion of confirmed PE in these patients is 10 and 30%, respectively.

More recently, another clinical decision rule, the YEARS algorithm, has been introduced, which is a strategy that incorporates differential D-dimer cutoff values upon presentation (presence of clinical signs of DVT, hemoptysis, and PE as the most likely diagnosis).[43] In contrast, the Pulmonary Embolism Rule-out Criteria has been proposed to identify patients with such a low probability of PE that diagnostic workup should not even be initiated.[44] In normal physiological conditions, around 2 to 3% of fibrinogen is converted into fibrin and then rapidly broken down by the fibrinolytic pathway. D-dimer values tend to increase physiologically with ageing, in pregnancy and the postpartum period (up to 6 weeks after delivery), and in renal insufficiency.[38] D-dimer levels increase following a VTE event. As mentioned, to avoid unnecessary imaging testing, age-adjusted cutoffs have been proposed (age $\times$ 10 µg/L, in patients aged >50 years) excluding PE and recently, a pregnancy-adapted algorithm has also been validated.[45,46] The use of this decision-making algorithm, which combines clinical probability assessment and D-dimer testing, results in a 30% reduction in an otherwise unnecessary imaging for suspected thromboembolic events. A systematic review and meta-analysis by Stals et al found that the age-adjusted D-dimer and the pretest-adjusted D-dimer can be considered safe (defined as the diagnostic failure rate, represented by the predicted 3-month VTE incidence after exclusion of PE without imaging at baseline) especially in patients with cancer, in older patients, and in those with a history of VTE.[47] Furthermore, efficiency (defined as the proportion of individuals classified by the strategy as "PE considered excluded" without imaging tests) was highest in a pretest probability-based strategy (YEARS) than an age-adjusted threshold strategy. Moreover, there is a lack of consensus among international guidelines providing recommendations on the use of D-dimer testing, excluding PE, particularly regarding the appropriate D-dimer threshold. A recent review by Fan et al reported that Seven guidelines (National Institute for Health and Care Excellence European Society of Cardiology and European Respiratory Society, European Association of Nuclear Medicine, Pulmonary Embolism Response Team consortium, American College of Emergency Physicians, American Society of Hematology, and American College of Physicians) recommended an age-adjusted cutoff of age $\times$ 10 µg/L when patients were >50 years; four guidelines provide no such recommendation (Thrombosis and Hemostasis Society of Australia and New Zealand, Japanese Circulatory Society, Prospective Investigation of Pulmonary Embolism Diagnosis II investigators, and British Thoracic Society), two guidelines recommend clinical probability adjusted cutoff (European Society of Cardiology and European Respiratory Society and Pulmonary Embolism Response Team) consortium), and two guidelines (UpToDate and SPAIN) recommend a conventional D-dimer cutoff of 500 µg/L.[48] In addition to the threshold changing depending on the recommendations used, clinicians using an algorithm integrating D-dimer values need to be aware of the limitations of this biological test. D-dimer is nonspecific, with several factors highly associated with "false" positive results such as malignancy, surgery, infections, immobilization, connective tissue disease, lung disease, etc.; all conditions characterized by local or systemic activation of blood coagulation and fibrinolysis. Furthermore, prolonged tourniquet placement leading to hemoconcentration and clot formation may jeopardize the quality of hemostasis testing, including D-dimer. Conversely, several conditions may lead to "false" negative D-dimer results such as small thrombus, long time has passed since the acute episode of thrombosis, DVT or isolated subsegmental PE, hypofibrinolytic state and anticoagulant therapy. D-dimer levels fall quickly after starting anticoagulation, with 25% decrease 24 hours after starting heparin therapy in patients with acute VTE.[38]

POCT D-dimer tests are now available, significantly reducing the time required to obtain results, which can range from 6 to 20 minutes depending on the technique used.[49] Although these tests are commercially available, their diagnostic performance generally appears inferior to the gold standard reference technique (i.e., ELISAs or immunochemiluminescent or immunofluorescence immunoassays). Furthermore, none of these tests have undergone validation through interventional clinical studies for implementation. These assays suffer from the disadvantage of significant variability in results, especially for measurements near to the 500 µg/L threshold. The validation of these thresholds indicated by suppliers for decentralized devices remains largely unproven. Additionally, the majority of these tests fail to meet the minimum sensitivity and NPV required for exclusion testing according to Clinical and Laboratory Standards Institute (CLSI) standards, unlike the VIDAS® Automated enzyme-linked immunofluorescence assays, widely considered the gold standard.[50] Therefore, the use of these POCT-D-dimer tests should be reserved for screening for thromboembolic disease only in patients with low pretest clinical probability, particularly in regions where access to conventional laboratory testing or imaging techniques such as ultrasound is limited to prevent unnecessary patient transfers between centers.[51]

If negative D-dimer is validated to rule out a thromboembolic event for patients with low or moderate probability of

 

DVT in the lower limb and PE, it may not hold true for more unusual thromboembolic events, such as CVT, SVT, or CRVO.

CVT is very rare, affecting around five people per million each year, and mainly occurs in young patients.[52] The use of D-dimer to rule out this diagnosis remains challenging. Although the NPV is over 99%, a significant rate of false negatives is observed, especially when headache is the single symptom, depending on duration of symptoms and the anatomic extent of thrombosed sinuses.[53]

SVT is associated with certain conditions such as liver cirrhosis, solid cancer, and intra-abdominal inflammatory diseases.[54] The existing publications have included highly heterogeneous populations: however, a recent meta-analysis investigating the use of D-dimer to rule out this condition has shown that D-dimer appears to have high sensitivity for diagnosing patients at high risk for SVT.[55] However, the meta-analysis found a lack of published studies evaluating patients at low risk of SVT. Accordingly, the authors concluded that D-dimer should not be used as a standalone test in patients presenting to the ED with acute abdominal pain to exclude SVT and further diagnostic imaging.

CRVO is a painless eye condition characterized by variable degrees of vision alteration, often leading to visual impairment. It is ranked among the leading causes of visual impairment, affecting over 16 million people worldwide. CRVO is frequently associated with underlying coagulation disorders (such as myeloproliferative disorders, Factor V Leiden thrombophilia, disturbances of the protein S and C pathways, antithrombin deficiencies). A prompt ophthalmologic examination, including visual acuity measurement, iris examination, and fundus examination, is essential for diagnosis and management. Close monitoring of the iris and retina is crucial to detect neovascularization, which may require treatment.

Apart from the diagnostic approach, which primarily involves measuring D-dimer in cases of suspected thromboembolic events, the assessment of thrombotic risk also applies to hospitalized patients or those requiring the application of a cast, for example, in cases of fractures. Scores like the Padua or the International Medical Prevention Registry on Venous Thromboembolism can be used to assess thrombotic risk in hospitalized acutely ill medical patients.[56] Similarly, the Thrombosis Risk Prediction following cast immobilization score is used to evaluate thrombotic risk after plaster cast application in traumatology.[57] None of these scores incorporate hemostasis tests that have been developed for this indication.

### Arterial Thromboembolism

The main pathologies related to arterial thrombosis are acute myocardial infarction (AMI) and stroke. Less common locations include peripheral arteries of the lower limbs, viscera, or heart chambers.[58] The main pathophysiological mechanisms explaining arterial thrombosis are atherosclerosis and embolism related to atrial fibrillation. Atherosclerosis development is enhanced by hypercholesterolemia, hypertension, cigarette smoking, diabetes mellitus, obesity, and a sedentary lifestyle.[59] The management of this disease will primarily rely on controlling identifiable risk factors. If an embolic origin is suspected, a thorough investigation to identify the source, mainly the heart, or the presence of a patent foramen ovale should be conducted. However, some medications are responsible for increased risk of arterial thrombosis, such as hormone treatments (estrogens and steroids), intravenous immunoglobulins, erythropoiesis-stimulating agents, and anticancer therapies like vascular endothelial growth factor inhibitors, fluorouracil, or tamoxifen. Just like venous thrombosis, the risk of arterial thrombosis is increased by certain diseases such as antiphospholipid syndrome, cancer, hematologic disorders or autoimmune disorders (rheumatoid arthritis, lupus, vasculitis) and, as observed during the pandemic, by certain infectious diseases such as coronavirus disease 2019.[60]

In an emergency setting, the diagnostic approach to arterial thrombosis will primarily focus on identifying the underlying cause ahead of performing hemostasis tests. Thus, the recommendations regarding the management of AMI advocate only the evaluation of hemorrhagic risk related to the need for antithrombotic treatment using platelet count and/or routine hemostasis assays (i.e., fibrinogen, prothrombin time [PT], aPTT),[61] while the guidelines for stroke management suggest conducting hemostasis tests only in some circumstances if there is suspicion of coagulopathy.[62]

## Blood Collection and Analytical Phase

Hemostasis tests have limited utility in evaluating both thrombotic and hemorrhagic risks and seldom change the management of noncritical patients in the ED. Otherwise, if these laboratory tests are performed, it is important for clinicians to evaluate their limitations and to collaborate with the laboratory to correctly interpret any abnormal values. It is important to bear in mind that the majority of errors in laboratory medicine occurs during the preanalytical phase (68%) rather than during the analytical (13%) and postanalytical phases (19%). Fortunately, 75% of these errors have no consequence for the patient.[63] The preanalytical phase is preceded by a five "rights" checkup called the pre-preanalytical phase. This checkup is carried out by the clinician and blood collector, who check if it is the right test for the right patient at the right time with the right sample and using the right transportation. The preanalytical phase includes all factors that influence test results before analysis. Many additional items are included, such as correct separation by centrifugation, appropriate pretreatment, correct aliquoting, sorting, and routing.[64] Clinicians or more commonly, emergency nurses, play a role in the preanalytical phase by ensuring that blood is drawn correctly and that a first discard tube is used only if necessary.

Recent recommendations for blood sampling in EDs from the European Society for Emergency Medicine, European Society for Emergency Nursing, and European Federation of Clinical Chemistry and Laboratory Medicine, have issued that the sampling posture should not be changed. If the patient has been lying for some time, blood should be

 

collected again in a lying position. They have also suggested verifying and registering the patient's fasting status, along with previous alcohol consumption.[11]

Blood should be collected by direct venous puncture with a 22- to 19-gauge needle, on distant sites from infusion catheters. A tourniquet should not be kept in place for more than 1 to 2 minutes before blood collection. To reduce the hemolysis rate, the use of straight-needle venipuncture or butterfly needles rather than sampling from IV catheters is recommended.[11] If a catheter is used for sampling, the first 10 mL of blood should be discarded. Blood samples should be drawn through new venipuncture in adult ED patients. In the process of placing a new peripheral venous catheter with a needle gauge $\leq$18, recent recommendations have suggested that blood samples could be drawn through the peripheral intravenous catheter, after carrying out a risk/benefit analysis, using the proper standard operating procedure and precautions to reduce hemolysis rate, such as the use of low vacuum tubes or tubes with manual aspiration.[11]

It is also important to observe the blood tubes order during sampling (i.e., the so-called "order of draw": blood culture bottles first, then serum tube without clot activator, then hemostatic tube, then serum tube with clot activator, then heparin tube, and finally ethylenediaminetetraacetic acid [EDTA] tube).[65] The discard tube is not necessary when drawing blood with a straight needle for the following tests: PT, or INR, aPTT, D-dimer, fibrinogen, and measurement of DOACs. Blood tubes must be completely filled (up to over 90% of their nominal fill volume) and then inverted slowly at least once before collecting the next tube, and when all tubes are collected and needle is removed from the patient vein, all tubes should be mixed for an additional four to six times, according to manufacturer's indications. Tube underfilling may bias laboratory test (due to the inappropriate blood-to-anticoagulant ratio), frequently leading to prolongation of coagulation times and D-dimer underestimation.[66]

Prehospital blood sampling, commonly performed in some countries, is considered acceptable as long as the collection and storage conditions meet minimum quality criteria, despite limited evidence demonstrating a reduction in TAT or the patient's length of stay in the ED.[11]

Laboratory analysis should be performed within 2 hours of sampling (4 h if centrifugation is performed). Centrifugation is generally performed using a force of 1,500 to 2,000 $\times$ G for 10 to 15 minutes at a controlled temperature between 15 and 25 °C.[67] In case of emergency, for PT, aPTT, D-dimer, fibrinogen, and DOACs measurements performed on fresh plasma, higher centrifugation forces ($>$2,000 $\times$ G) and shorter time ($<$10 min) could be considered. Transport of blood tubes to the laboratory must be as gentle as possible. Noncompliance with these procedures may trigger hemolysis, which can significantly interfere with some test results.[68] However, using a pneumatic transport system for sample transportation from the ED to the laboratory could be considered to reduce the TAT and length of stay, especially when EDs are dependent on a central laboratory that is not located near the ED.[11] However, such systems may affect platelet function, and should not be used when platelet function testing is planned.

Other clinical abnormalities, such as jaundice or hypertriglyceridemia must be detected at this point if they have not been reported by clinicians, as they can interfere with reagents and modify coagulation test results.[69]

The last checkup phase is the postanalytical phase. It includes comments on sample quality that might compromise the results, sample suitability concerning acceptance/rejection criteria, and interpretative comments accompanying test results.[70]

## Hemostasis Laboratory Tests

Laboratory tests easily accessible for hemostasis evaluation or anticoagulation monitoring in an emergency setting are complete blood count, standard coagulation tests (fibrinogen, aPTT, and PT or INR), fibrinogen, and anti-Xa assays. Some hospitals also have access to viscoelastic tests (VETs) and other POCTs such POCT-INR which have advantages in certain clinical situations where results are needed as quickly as possible. The main available POCTs and standard hemostasis tests are summarized in the ►**Table 1**.

As mentioned earlier, it is crucial to incorporate the clinical context into the request for hemostasis tests to prevent erroneous interpretations. For example, VKAs such as warfarin, acenocoumarol, and phenprocoumon interfere with the production of vitamin K-dependent coagulation factors (II, VII, IX, X). Rivaroxaban, apixaban, and edoxaban are direct inhibitors of factor Xa, while dabigatran is a direct thrombin (i.e., factor IIa) inhibitor. Parenteral anticoagulants such as heparins are inhibitors of both factor IIa and Xa. It is also important to bear in mind that standard coagulation tests were originally designed for diagnosing congenital deficiencies in coagulation factors, and their use in the context of nondrug-related acquired coagulopathies lacks well-established foundation.

### Primary Hemostasis

Primary hemostasis is not usually assessed by standard laboratory tests performed in most laboratories except for platelet count. Primary hemostasis can be globally evaluated by first-line platelet function testing such as Platelet Function Analyzer (PFA)-100/200. The PFA-100/200 test is carried out by aspirating whole blood through an orifice in a membrane covered with a reagent mixture (ADP/epinephrine or ADP/collagen), the time to orifice occlusion is then measured with prolongation of closure time potentially reflecting platelet abnormalities of number and/or function.[71]

The PFA-100/200 test is mainly sensitive to von Willebrand factor (VWF), another significant contributor to primary hemostasis. The PFA-100/200 test is useful to exclude von Willebrand disease (VWD) and severe inherited platelet function disorders.[71,72] The diagnosis of VWD will be made by measuring VWF antigen and/or platelet-dependent VWF activity, FVIII coagulant activity, VWF–FVIII binding, and genetic testing.[73] In addition, POCT which assess platelet function (like Multiplate analyzer, Verify Now, and whole-blood TEG® Platelet Mapping™ assay) are available. The only remaining indication for these POCTs to monitor P2Y12

 

**Table 1** Summary of the main indications for available point-of-care testing and hemostasis test in the emergency department

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|---|---|---|
| **A. Available POCT with their main indications and limits** | | |
| POCT-D-dimer | Indications | Patient with low pre-test clinical probability in poor imaging access area |
| | Limits | Unproven threshold, insufficient negative predictive value |
| POCT-INR | Indications | Patient on VKA with major bleeding or ischemic stroke before thrombolysis |
| | Limits | INR imprecision and overestimation especially in supra-therapeutic ranges, does not allow detection of low concentrations of DOACs, close to hemostatic safety thresholds |
| POCT-fibrinogen | Indications | Detection of hypofibrinogenemia during post-partum hemorrhage |
| | Limits | Available but no clinical performance data |
| Viscoelastic testing | Indications | Guiding transfusion management in trauma patients and post-partum hemorrhage |
| | Limits | Requires pre-established decision-making algorithms |
| POCT platelet function | Indications | Determine the timing of surgery for patients receiving P2Y12 inhibitors |
| | Limits | Instruments not interchangeable, preanalytical constraints (influence of platelet count and hematocrit) and not well evaluated analytical and clinical performances |
| POCT-DOAC | Indications | Rule out significant blood concentrations of DOAC in patients with acute ischemic stroke, severe bleeding, or those undergoing urgent surgical procedures |
| | Limits | Not all readily available |
| **B. Main indication for hemostasis tests in ED** | | |
| D-dimer | Suspected thromboembolism with low or intermediate probability | |
| INR | VKA monitoring | |
| aPTT | Suspected factor deficiency or monitoring of intravenous treatment with unfractionated heparin | |
| TT | Exclude clinically significant dabigatran levels (>30 ng/mL) if calibrated anti-IIa assay is unavailable | |
| Fibrinogen | Targeting fibrinogen administration in patient with active bleeding when plasma fibrinogen levels fall below 1.5 g/L | |
| Anti Xa assay | LMWHs | Detect an overdose and/or accumulation in case of bleeding |
| | UFH | Monitoring intravenous treatment with unfractionated heparin |
| | DOACs | Guide administration of reversal agents for critical scenarios such as bleeding or urgent surgery, Rule out significant DOAC level |

Abbreviations: aPTT, activated partial thromboplastin time; DOAC, direct oral anticoagulant; ED, emergency department; INR, international normalized ratio; LMWH, low molecular weight heparin; POCT, point-of-care testing; TT, thrombin time; UFH, unfractionated heparin; VKA, vitamin K antagonist.

inhibitors is to determine the timing of surgery.[74,75] There are major differences between the different platelet function tests, which are thus not interchangeable. In different studies that used several platelet function tests, some were associated with occurrence of clinical events and others not, partly because the platelet function tests did not explore the same aspects of platelet function. In addition, platelet function tests have preanalytical limitations, and their analytical performances have not always been well-evaluated. Some platelet function tests using whole blood can be influenced by variables such as platelet count and hematocrit.[76] For example, multiple electrode aggregometry measures the decrease in electrical impedance between two electrodes after platelet activation. These tests cannot be interpreted if the number of platelets is lower than $100 \times 10^9$/µL or if hematocrit is below 25%. Additional investigation of platelet function usually involves complex tests with a longer TAT only performed in specialized hemostasis laboratories.

## Secondary Hemostasis

Secondary hemostasis reflects a cascading activation of various coagulation factors leading to the final endpoint formation of fibrin. This cascade is composed of different pathways. The "contact pathway" is evaluated by measuring the aPTT. It provides information on all coagulation factors, except FVII. Within this test, an extract from rabbit or bovine brain containing various types of phospholipids serves as the surface for the elaboration of the prothrombinase complex. An activator of the contact system is also included in the reagent such as celite, kaolin, ellagic acid, or micronized silica particles. The aPTT is prolonged in case of qualitative and/or quantitative defects of fibrinogen, prothrombin, FV, FX, FVIII, FIX, FXI, FXII, and prekallikrein.

A second pathway is the tissue factor pathway. It is evaluated by measuring PT/INR. In this test, as for the aPTT, blood is collected into sodium citrate tubes and the sample is centrifuged to obtain citrated platelet-poor plasma.

 

The PT reagent—tissue thromboplastin (a mixture of recombinant tissue factor and phospholipids) suspended in calcium chloride—is added to the test plasma sample to stimulate the tissue factor pathway. The PT is prolonged by qualitative and/or quantitative defects in fibrinogen, prothrombin, FV, FX, and FVII. The PT is expressed in seconds needed for the clot to develop, and can be mathematically converted into the INR using the formula: $INR = (PT/MNPT)^{ISI}$ (where the PT is the patient PT, the MNPT is the mean normal PT of a normal population, and the ISI is the International Sensitivity Index). The ISI is assigned to the reagent by the manufacturer, as validated by the laboratory, based on various approaches.

The INR has no measuring unit, and was designed only for monitoring anticoagulant therapy (VKA; which impair FII, VII, IX, X function). The normal range of INR in healthy subjects is around 0.8 to 1.2. The therapeutic range for VKA therapy ranges from around 2.0 to 3.0. The higher the INR value above this range, the greater is the risk of bleeding in patients on VKA therapy.

In a VKA-treated patient with severe bleeding and an INR > 1.5 (>1.2 if intracranial hemorrhage), it is recommended to stop anticoagulant therapy and antagonize it by administering prothrombin complex concentrate (PCC).[77] It is also recommended to check the INR within 30 minutes at 6 to 8 hours and 24 hours after antagonization, to decide on further administration of PCC.[78]

Obtaining INR results quickly is crucial in certain conditions for patients taking VKAs. POC-INR testing enables immediate bedside measurement using venous or capillary blood samples. These rapid results are particularly valuable for patients experiencing major bleeding, where potential VKA reversal is necessary, or ischemic stroke, where promptly ruling out a significantly elevated INR and administering thrombolytic therapy is essential.[79] POCT-INR tests tend to overestimate INR levels, approximately 0.3 higher than laboratory INR, especially in supratherapeutic ranges. The imprecision of POCT results can be critically important, especially in cases like stroke. Stroke management guidelines recommend thrombolytic therapy within 4.5 hours after stroke onset for patients on warfarin therapy only if their INR is below 1.7.[80] Consequently, if a POCT overestimates INR, patients presenting with a stroke may be excluded from thrombolysis, whereas they might have been eligible if a standard INR measurement had been utilized. Despite this, POC-INR has proven to be useful in emergency situations where a TAT of 60 minutes is considered too long or cannot be achieved with standard tests.[81]

Another pathway sometimes referred to is the common pathway, which includes the transformation of prothrombin to thrombin and fibrinogen to fibrin by factors Xa and Va. This pathway is evaluated by both the aPTT and the PT.

Among the Caucasian population, VWD represents the most prevalent hemostasis abnormality. In these patients, the aPTT will mostly be normal, except in those types associated with factor VIII deficiency. This is since FVIII is normally protected by VWF, and thus low levels of VWF can lead to low levels of FVIII and thus prolongation of aPTT.

If coagulation times are unexpectedly abnormal, the initial steps, as mentioned before, should be the exclusion of anticoagulation therapy and any preanalytical error by investigating blood sampling conditions before considering the possibility of a medical condition.

If the aPTT is prolonged with a normal PT, the potential diagnosis is contact factor deficiency or inhibitor (VIII, IX, XI or XII), VWD, lupus anticoagulant, or heparin anticoagulant.

If the aPTT is normal but the PT is prolonged, the potential diagnoses are VKA therapy or factor VII deficiency. Lippi et al and others have previously summarized the different causes (physiological, pathological, therapeutic, and spurious) for coagulation time shortening and prolongation (►**Table 2**).[82,83]

If both aPTT and PT are prolonged, the potential diagnoses include DIC, sepsis, treatment with heparin/DOACs/warfarin, factors deficiency (especially II, V, X), combined factors deficiency (e.g., FVIII and FV), fibrinogen deficiency, or severe liver disease.[24]

With the commercialization of DOACs since the 2010, the interpretation of hemostasis tests has become increasingly intricate. Conventional coagulation tests are neither recommended for assessing DOACs concentration, nor for excluding the presence of DOACs, but it is essential to consider the use of DOACs when interpreting coagulation test results. Previous studies have shown that PT and aPTT within normal range are not suited to safely exclude clinically relevant DOAC concentrations (i.e., 30 ng/mL before surgery or an invasive procedure with high bleeding risk).[84] Similarly, POCT devices based on measurement of PT and aPTT cannot be used to exclude clinically relevant DOAC concentrations to guide thrombolysis, for example. In fact, POCTs measuring INR (CoaguChek-POCT) are sensitive to DOACs, but their sensitivity does not allow detection of low concentrations of DOACs, close to hemostatic safety thresholds (i.e., typically between 30 and 50 ng/mL).[85] The same conclusions can be drawn from studies conducted with activated clotting time (Hemochron Signature Elite® cartridge high range and low range).[85] In addition, these POCTs are not specific for DOACs, and other causes of prolonged coagulation times should be considered if the presence of the drug is only supposed, or if DOAC-related anticoagulation coexists with other pathologic conditions (such as dilutional or consumption coagulopathy leading to low fibrinogen level and platelet count/function). Therefore, many confounders render the positive predictive value of these tests not worth considering.[86] POCTs for the specific screening or measurement of DOACs are currently being developed, but have not yet been validated. Viscoelastometric tests measure parameters correlated with circulating DOACs concentrations, but are not sensitive to low DOAC concentrations and cannot exclude presence of active drug.[87] The currently recommended laboratory approach for patients on DOACs is measuring the anticoagulant drug plasma activity by means of drug-calibrated anti-FX assays in the case of FXa inhibitor (i.e., apixaban, rivaroxaban, edoxaban), or by means of drug-calibrated anti-FIIa assays in the case of thrombin inhibitors (i.e., dabigatran), which display a linear relationship with the presence of active drug concentration in plasma. In resource-limited centers that

 

**Table 2** Summary of the various factors leading to both shortened and extended coagulation times

| A. aPTT | | | |
|---|---|---|---|
| **Shortening** | | **Prolongation** | |
| Physiological | Pregnancy | Physiological | None |
| | Physical exercise | | FXII deficiency |
| | Ageing | Pathological | FXI, FIX, FVIII deficiencies |
| Pathological | Venous thrombosis | | FII, FV, FX deficiencies |
| | Acute coronary syndrome | | von Willebrand disease |
| | Cancer | | Lupus anticoagulant |
| | Sepsis | | Disseminated intravascular coagulation |
| | Diabetes | | In vivo acidosis (with Actin FS reagent) |
| | Liver and thyroid disorders | Therapeutic | UFH |
| Therapeutic | Recombinant activated FVII | | Dabigatran |
| Spurious | Prolonged venous stasis | | Anti-XI(a) drugs (i.e., asundexian) |
| | Vigorous mixing of blood tubes | | Overdose of VKA, LMWH, or anti-Xa drug |
| | Spurious coagulation of the sample | Spurious | Heparin and/or EDTA contamination |
| | Incomplete platelets separation | | Incomplete filling |
| | Loading into long track-lines | | Hyperbilirubinemia, hypertriglyceridaemia |
| | Analytical error | | Delayed separation |
| | | | Analytical error |
| | | | Hemolysis |
| **B. PT-INR** | | | |
| **Shortening** | | **Prolongation** | |
| Physiological | Pregnancy | Physiological | None |
| | Aging | Pathological | Vitamin K deficiency |
| | Physical exercise | | Deficiencies of FVII, FV, FX |
| Pathological | Venous and arterial thrombosis | | Liver disease |
| | Cancer | | Afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia |
| | Sepsis | | Disseminated intravascular coagulation |
| | Thyroid disorder | Therapeutic | Dabigatran |
| Therapeutic | Recombinant activated FVII | | Anti-FXa drugs |
| | Estrogen-containing medications | | Warfarin and other VKAs |
| Spurious | Prolonged venous stasis | Spurious | Heparin and/or EDTA contamination |
| | Hyperbilirubinemia, hypertriglyceridemia | | Analytical error |
| | Spurious coagulation of the sample | | Use of centrifuge brake |
| | Incomplete platelets separation | | |
| | Loading into long track-lines | | |
| | Sample rerun after freezing | | |
| | Analytical error | | |

Abbreviations: aPTT, activated partial thromboplastin time; EDTA, ethylenediaminetetraacetic acid; INR, international normalized ratio; LMWH, low molecular weight heparin; PT, prothrombin time; UFH, unfractionated heparin; VKA, vitamin K antagonist.

lack tests for drug-calibrated anti-FIIa assays, the TT is useful to exclude clinically significant dabigatran levels (>30 ng/mL).[88] The TT is able to determine drug presence, although prolongation of the TT is not specific to dabigatran and should not be used to assess dabigatran concentrations in the normal therapeutic range.[89] This is helpful in ED cases with bleeding, where the clinical question is whether there are significant levels of dabigatran that require reversal, or on the contrary to rule out contraindications to thrombolysis due to anticoagulation in cases of ischemic stroke among

 

patients receiving dabigatran.[90] In the same applications, DOAC Dipsticks have been developed to detect DOACs (apixaban, rivaroxaban, and dabigatran) in urine. However, it is important to note that a positive result of DOAC Dipstick may not always indicate a clinically significant DOAC concentration in the plasma at the time of testing. Additionally, Dipstick results can be influenced by urine color, the presence of blood cells in urine, and duration of urine retention in the bladder before sample collection. Therefore, this test has its limitations. On the other hand, a negative result on the DOAC Dipstick can be considered clinically reliable, and is therefore useful for ruling out the presence of DOACs.[91]

Certain conditions such as DIC or liver disease also lead to significant alterations in coagulation tests, thus making their interpretation sometimes challenging. DIC is characterized by systemic coagulation activation leading to diffuse microvascular thrombi, organ dysfunction, and depletion of coagulation factors and platelets. DIC occurs as a complication of various underlying disorders, including severe infections, cancer, pregnancy complications, or major organ or tissue injury. The diagnosis of DIC can be challenging. Therefore, the ISTH has proposed a scoring system which includes platelet count, INR, fibrinogen, and D-dimer (a resulting score of $\geq$5 is compatible with overt DIC).[92] In 2017, ISTH introduced the sepsis-induced coagulopathy (SIC) scoring system (based on platelet count, PT and Sequential Organ Failure Assessment [SOFA] score) to detect an earlier stage of DIC.[92]

Advanced cirrhosis is a condition that also affects hemostasis tests. This liver disorder results in reduced synthesis of all coagulation factors, except FVIII, and a decrease in the production of the anticoagulant proteins C and S. As a result, cirrhotic patients are in a finely balanced but fragile hemostatic state, and they can lean towards either a bleeding or thrombotic tendency. INR values are often elevated in cirrhotic patients without necessarily indicating an increased risk of bleeding. In fact, attempts to correct INR in cirrhotic patients experiencing bleeding episodes have been shown to increase mortality and risk of thrombosis.[93,94] Other chronic disorders such nonalcoholic fatty liver disease are associated with an increased thrombotic risk. Standard laboratory coagulation tests are of limited utility in these patients.[95]

## Factor Level Measurement

The measurement of coagulation factors is useful in cases of bleeding diathesis and prolonged aPTT to exclude underlying diseases related to factor deficiencies, especially VWD, hemophilia A (FVIII deficiency) or hemophilia B (FIX deficiency), and FXI deficiency. In the absence of bleeding diathesis and prolonged aPTT, lupus anticoagulant or FXII deficiency may be the cause. Coagulation factor testing can also be relevant in cases of liver disease but this is still debated. Indeed, both acute and chronic liver failure can disrupt standard hemostasis tests. Reduced liver synthesis of coagulation factors due to liver disease leads to prolongation of PT and aPTT. This deficiency in coagulation factors is accompanied by a decrease in the synthesis of anticoagulant proteins (especially protein C and S), thereby shifting the hemostatic balance towards a more thrombotic state.[96] In cirrhotic patients, this phenomenon explains the occurrence of splanchnic venous thromboses. Since coagulation tests do not assess deficiencies in anticoagulant proteins, they should be interpreted with this limitation in mind. In cases of acute liver failure, measuring factor V levels may be useful for assessing the severity of hepatic functional impairment, where the question of liver transplantation arises. Recognized predictive criteria by Eurotransplant include the King's College criteria for acute liver failure due to paracetamol intoxication and the Clichy criteria for hepatitis B virus-induced acute liver failure.[97] An FV level below 20% for patients under 30 years of age, and below 30% for patients aged 30 or older, is a severity criterion indicating the need for liver transplantation. Unfortunately, factor level measurement is not available stat in all laboratories, and some authors have recently proposed alternatives such as the Model for End Stage Liver Disease or the Liver Chronic Liver Failure-SOFA score.[98]

## Fibrinogen

The final step in the coagulation cascade involves the conversion of fibrinogen into insoluble fibrin polymers through the action of the protease thrombin, resulting in the formation of a clot. Following polymerization and factor XIII-mediated cross-linking with activated platelets during primary hemostasis, fibrin and platelets form a plug that is resistant to mechanical or enzymatic disruption, ensuring vascular integrity and hemostasis in the event of vascular damage. A fibrinogen level of 1 g/L is considered adequate to prevent bleeding, with normal range typically spanning between 1.6 and 4 g/L. Hypofibrinogenemia or dysfibrinogenemia can be either acquired or congenital. Congenital afibrinogenemia is rare, with estimated prevalence of approximately 1 in 1,000,000, while dysfibrinogenemia and hypofibrinogenemia are more common and usually asymptomatic.[99] Acquired causes of low fibrinogen levels include hemodilution resulting from massive transfusion, reduced synthesis in patients with liver impairment, or increased consumption in conditions such as sepsis, DIC, or cancer. Acquired dysfibrinogenemia is primarily caused by formation of autoantibodies in patients with myeloma or autoimmune diseases.[100] Hypofibrinogenemia is also observed in patients with coagulopathy after trauma, postpartum hemorrhage, or gastrointestinal bleeding.[101] To prevent major hemorrhage and death, European guidelines recommend administering fibrinogen, via fibrinogen concentrates or cryoprecipitates as available, to patients with active bleeding when plasma fibrinogen levels fall below 1.5 g/L.[102] The most commonly used laboratory method for measuring fibrinogen is the Clauss assay, which evaluates fibrinogen ability to create a fibrin clot when exposed to thrombin, and is hence both a quantitative and qualitative test.[103] Notably, pseudohypofibrinogenemia might occur when the patient is undergoing treatment with a direct thrombin inhibitor such as dabigatran. Moreover, the Clauss fibrinogen assay includes heparin inhibitor that may be overridden when the blood contains elevated levels of unfractionated heparin (UFH).

 

## Platelet Count

The platelet count plays a crucial role in evaluating hemostasis, with normal ranges between 150 and $400 \times 10^9$/L. A decreased platelet count may increase the risk of bleeding, while an elevated count can be associated with an enhanced risk of thrombosis. Significant bleeding rarely occurs with platelet count $>30 \times 10^9$/L, and major bleeding is typically limited to patients with platelet count $<10 \times 10^9$/L.[104] The risk of thrombosis associated with thrombocytosis is more dependent on the underlying cause rather than the absolute platelet count.[105]

### Thrombocytosis

Thrombocytosis does not demand immediate treatment in the emergency setting. However, the primary purpose of the medical evaluation will be to determine its underlying cause to facilitate appropriate treatment. Thrombocytosis can be categorized into three etiological categories: reactive, clonal, or spurious.[105] Reactive thrombocytosis, which is secondary to conditions such as infection, inflammation, hyposplenism, malignancy, hemolysis, iron deficiency, or drug effects, is generally associated with low risk of thrombosis. Clonal thrombocytosis is more commonly linked to thrombotic events and includes myeloproliferative diseases such as essential thrombocythemia, chronic myeloid leukemia, myelofibrosis, and others. It should be noted that extreme thrombocytosis can also increase the risk of bleeding, often due to acquired VWD.[106] Spurious thrombocytosis is identified by the presence of nonplatelet structures (cryoglobulinemia, neoplastic cells, schistocytes, bacteria, etc.) in the peripheral blood, which are counted as platelets by automated hemocytometers.[107]

### Thrombocytopenia

If thrombocytopenia is detected during blood testing, the first step will be to examine the peripheral blood smear to exclude platelet clumping, an in vitro phenomenon related to presence of EDTA as additive in the test tube generating pseudothrombocytopenia.[107] Confirmation of platelet count is achieved by analyzing the sample using a different anticoagulant (i.e., sodium citrate) or warming the sample immediately upon collection (to exclude the effect of cryoglobulins).

The origin of thrombocytopenia can be attributed to either a deficiency in platelet production from the bone marrow (central origin) or to circulating platelet destruction/sequestration (peripheral origin). If bicytopenia or pancytopenia is present, central causes can be benign (folic acid or vitamin B12 deficiency) or malignant (acute leukemia or myelofibrosis). The main central causes related to isolated thrombocytopenia are toxic (trimethoprim, chlorothiazide, etc.), viral (mumps, rubella, varicella, etc.), linked to acute alcohol abuse or due to intrinsic megakaryopoiesis defect. Peripheral thrombocytopenia is mainly infectious (platelet consumption due to inflammation-induced coagulation), toxic (quinine, heparin, etc.), or immune (immune thrombocytopenic purpura, lupus, etc.).[108] The laboratory tests that will help to make a diagnosis explaining thrombocytopenia include optical microscopy of the peripheral blood film, assessment of immature platelet fraction (increased in case of a peripheral cause), viral serology (human immunodeficiency virus, Hepatitis C virus, cytomegalovirus, etc.), and the presence of hemolysis features (schistocytes, increased lactate dehydrogenase, bilirubin, D-dimer, etc.).[109] If thrombocytopenia is unexplained or suspected to result from a deficiency in platelet production within the bone marrow, it is recommended to conduct an examination of the bone marrow through aspiration and biopsy.

Several hematological emergencies can be associated with thrombocytopenia, such as purpura fulminans or thrombotic microangiopathies.

Purpura fulminans occurs as a result of a severe infection, predominantly caused by *Meningococcus* or *Streptococcus*, and carries a mortality rate of 20 to 60%. This syndrome is characterized by the combination of DIC and endovascular thrombosis. Prompt action is necessary, starting with blood culture collection, followed by immediate intravenous administration of antibiotics.

The most common thrombotic microangiopathies are thrombotic thrombocytopenic purpura (TTP) in adults and hemolytic–uremic syndrome (HUS) in children and young adults. TTP typically presents with thrombocytopenia, microangiopathic hemolytic anemia, fluctuating and reversible neurological disturbances, and in 40% of cases, fever and kidney failure. In acquired cases, this microangiopathy is caused by the presence of an antibody that inactivates ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a VWF cleaving protease. In case of a high French or PLASMIC score, measurement of ADAMTS-13 activity is crucial for achieving a final diagnosis.[110,111] The availability of ADAMTS-13 testing in medical laboratories is increasing due to the recent commercialization of rapid and automated immunoassays.[112] Treatment involves the administration of corticosteroids, rituximab, and therapeutic plasma exchange.[113] HUS is a triad characterized by hemolytic anemia with schistocytes, thrombocytopenia, and acute renal failure. HUS is most commonly caused by an infection due to toxin-producing *Escherichia coli* bacteria and is also treated with plasmapheresis.[114]

*Measuring Anticoagulants Using Anti-Xa and Anti-IIa Assays*

Chromogenic assays measuring the activity of activated clotting factors are available to monitor the effect of anticoagulants. They are calibrated against each anticoagulant to provide an estimation of plasma concentration of that anticoagulant from the activity measured. The antifactor Xa assay is used for monitoring the pharmacodynamic effect of LMWHs in inhibiting FXa, especially for specific patient categories such as those with extreme weights or renal insufficiency. However, it is not recommended as part of routine practice, since LMWH therapy does not normally need to be monitored.[115] Additionally, the test serves as a mean to monitor intravenous treatment with UFH in specific hospitalized patients, although the aPTT is more widely used for this purpose.

Calibrated anti-Xa and anti-IIa are used to assess the effect of DOACs. Since their commercial approvals in 2010, DOACs

 

have expanded their indications, particularly in treatment and prevention of thromboembolism in various cardiovascular contexts. These medications offer the advantage of more predictable pharmacokinetic and pharmacodynamic profiles compared to VKAs, and they do not require routine coagulation monitoring.

However, there are situations where assessing anticoagulation activity becomes necessary to guide physicians, for example, in administering reversal agents for critical scenarios such as bleeding, urgent surgery or before pharmacological thrombolysis. If a patient requiring urgent intervention has a drug concentration exceeding 30 ng/mL and is at a high risk of bleeding, reversal agent administration is likely warranted. In cases of serious bleeding, antidote administration should be considered if the drug concentration exceeds 50 ng/mL.[116] For acute ischemic stroke, the current European guidelines discourage the use of intravenous thrombolysis for patients who have been on DOAC therapy within the last 48 hours, unless calibrated tests are available. However, mechanical thrombectomy appears to be safe for patients with large vessel occlusion.[117] According to Seiffge et al,[118] for patients who have taken a DOAC within the past 48 hours, it is recommended to administer idarucizumab before thrombolysis when the concentration of dabigatran exceeds 30 ng/mL. In the case of FXa inhibitors, intravenous thrombolysis is recommended if the drug-specific anti-Xa level is below 30 ng/mL. If the level is between 30 and 100 ng/mL and the disability is severe, thrombolysis should be considered. Administration of andexanet alfa, an antidote of FXa inhibitors, is worth considering despite its high cost and lack of reimbursement by many health insurance companies. While this treatment effectively reduces anti-Xa activity by 90%, it is important to note the occurrence of FXa activity rebound after infusion, as well as a 10% incidence of early thrombotic complications.[119]

### Viscoelastic Tests

VETs offer an alternative to standard coagulation tests for guiding the administration of hemostatic agents and blood products in the setting of acute bleeding. Indeed, standard coagulation testing in most clinical laboratories prioritizes accuracy over TAT, whereas viscoelastic methods provide information within a short time frame (usually within 15 min for the main parameters) about the contribution of coagulation factors, fibrinogen and platelets to the mechanical properties of the clot, and about the degree of activation of fibrinolytic system. They enable clinicians to quickly assess the hemostatic status, helping to determine whether the bleeding may be due to a defect in the hemostatic system, or if not, to provide additional support for an invasive procedure. Additionally, they offer the advantage of being readily available directly in the ED. This allows for the determination of which blood product must be administered immediately to correct any potential hemostatic defect, but the interpretation of outcomes should be combined with the use of preestablished decision-making algorithms. In cases of trauma-associated coagulopathy, standard laboratory testing (such as PT/aPTT, fibrinogen) are performed together with viscoelastic testing. The selection of the appropriate method hinges on the requirements and capacities of the specific institution, prioritizing both rapid generation of test results and necessary precision to inform clinical decisions regarding the requisition of blood products for addressing hemostatic defects associated with bleeding. Various forms of VET are available: thromboelastography (TEG), rotational thromboelastometry (ROTEM), ClotPro system, and Quantra QStat System.[120] Each device has different measurement principles and reagents, which means that specific threshold values for each device must be used. Viscoelastic monitoring is a technique of ex vivo clotting that provides visual information from uncentrifuged whole blood regarding most of the whole hemostatic process (from clot formation to fibrinolysis) including in some cases the contribution of platelets. However, it is insensitive to primary hemostasis, to natural anticoagulants and to moderate hyperfibrinolysis.[121] VET, like other POCTs, presents several challenges, including the potential for interuser variability due to lack of training, paucity of level 1 evidence from high-quality randomized controlled trials, and noninterchangeable results between different technologies (e.g., TEG® and ROTEM®), as well as between different device models. VET is not well-suited for detecting hypercoagulability, since it is unaffected by antithrombin, and proteins C and S levels and frequent hemorrhagic diseases (minor hemophilia, VWD, and other mild bleeding disorders).[9] They present more variation and worse precision compared to standard assays, but provide a reliable estimation of the clinical situation and needs, which would theoretically make them advantageous in certain situations.[122,123] Their use is currently suggested to guide the use of hemostatic agents and blood products in cardiac surgery, liver transplants, trauma patients, and postpartum hemorrhage.[124]

## Significant Hemorrhage in the Emergency Department

Upon ED admission, some patients present with significant bleeding, thus necessitating close collaboration between clinicians and laboratory biologists for effective management. Critical bleeding refers to intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular bleeding with compartment syndrome, or an ongoing bleed that leads to hemodynamic instability (a decrease in systolic blood pressure of 20 mm Hg or systolic blood pressure $<$90 mm Hg) or respiratory compromise (respiratory rate $>$30 breaths per min, oxygen saturation $\leq$92%, requiring invasive or noninvasive mechanical ventilation).[125] These major bleedings will result in a disrupted balance between coagulation and fibrinolysis, characterized by impaired clot formation leading to spontaneous, prolonged, or excessive bleeding, as well as to a thrombotic tendency. This phenomenon, exacerbated by acidosis and hypothermia, is termed coagulopathy.[126] Early recognition of coagulopathy is crucial for prompt and successful management and improved clinical outcomes after major blood loss.

 

## Trauma-induced Coagulopathy

The primary cause of death following severe hemorrhage worldwide is trauma. The concept of trauma-induced coagulopathy (TIC), indicating abnormal blood clotting capacity resulting from trauma, has been extensively studied in recent decades. Tissue injury and shock collaborate to activate the endothelium, platelets, and the immune system, releasing various mediators that decrease fibrinogen, disrupt platelet function, and hinder thrombin generation. The compromised hemostatic capacity may fluctuate between hypocoagulation (in the early hours following the trauma) and hypercoagulation leading to thromboembolic events (typically beyond 24 h after the injury).[126] The disturbance in coagulation is further intensified by increased fibrinolysis through plasmin generation, ongoing blood loss, hemodilution, metabolic acidosis, and hypothermia. During the management of a trauma patient, the infusion of significant amounts of cold fluids and blood products leads to the dilution of enzymes essential for clot formation and exacerbates hypothermia, impairing both clotting factor activity and platelet function. This collectively forms what is sometimes referred to as "resuscitation-associated coagulopathy."[127]

In such critical scenarios, repeated hemostasis monitoring is recommended, either through conventional laboratory tests (PT/INR, fibrinogen, platelet count) or through viscoelastic testing. For trauma patients, threshold values of PT ratio greater than 1.2 and 1.4 have been suggested to indicate moderate and severe impairment of coagulation, respectively.[128] Baksaas-Aasen et al proposed diagnostic thresholds for TIC which include an INR $>1.2$, fibrinogen $<2.0$ g/L, and thrombocytopenia (platelet count $<100\times10^9$/L).[129] As stopping the bleeding remains mainstay of clinical management, hemorrhage control includes restricted fluid replacement with warm crystalloids, early administration of tranexamic acid, and red blood cell transfusion for achieving hemoglobin levels of around 70 to 90 g/L.

The administration of fresh frozen plasma guided by VETs or conventional laboratory tests, fibrinogen supplementation if the level drops below 1.5 g/L, platelet transfusion to target a threshold of at least $50\times10^9$/L and $100\times10^9$/L may be advisable in case of cerebral hemorrhage. If necessary, calcium administration is recommended to ensure the maintenance of ionized calcium levels within the normal range. Implementing goal-directed therapy, which includes an early massive transfusion protocol within the first hour and quick transitions to a goal-directed transfusion strategy using VET, is likely the current best approach to reduce inappropriate transfusions in real-world settings.[130]

## Heat Stroke Coagulopathy

Heat stroke is a critical condition marked by a core body temperature exceeding 40.5 °C (>105 °F). This heightened temperature can result from intense physical activity or exposure to extreme weather conditions with high ambient temperatures. The incidence of heat stroke is expected to rise in the coming years due to climate changes, characterized by more frequent and intense heatwaves. The pathophysiology of heat stroke involves a complex interaction of factors including heat cytotoxicity, coagulation, and inflammation, leading to systemic injury and multiorgan failure. This heat-induced disruption of normal hemostasis is termed heat stroke-induced coagulopathy (HSIC). Hyperthermia causes microvascular endothelial cell damage, leading to the activation of the endogenous coagulation pathway and intravascular microthrombosis.[131] It manifests with several abnormalities in hemostasis tests, such as thrombocytopenia, prolonged PT and aPTT, high D-dimer levels, prolonged clotting times, increased fibrin degradation products, endothelial damage indicated by increased soluble thrombomodulin, leukopenia with decreased neutrophils, increased thrombin–antithrombin complexes, and reduced plasma levels of antithrombin, proteins C and S.[131,132]

HSIC can progress to DIC and multiorgan failure if severe enough. As for sepsis (and the SIC score), there is a need for criteria for helping physicians to diagnose and decide the treatment of HSIC as soon as possible.[132]

## Snakebite Envenomation Coagulopathy

Venom-induced consumption coagulopathy (VICC) stands as the primary systemic consequence of snake envenomation, posing a significant public health concern, particularly for impoverished farming communities in rural tropics and subtropics. The prevalence of reported hemotoxic presentations is as follows: coagulopathy (43.8%), systemic bleeding and hemorrhage (23.8%), thrombocytopenia (18.7%), hematuria (14.1%), and hematemesis (4.1%).[133] While VICC shares similarities with DIC, including elevated D-dimer levels, prolonged PT, and low fibrinogen levels, it notably differs by lacking systemic microthrombi, end-organ failure, rapid onset and resolution, and exhibiting lower mortality rates.[134] The venom's toxins swiftly deplete clotting factors, inducing coagulopathy, and inflict damage upon blood vessel walls, heightening the risk of bleeding. The coagulopathy may then by worsened by the development of systemic infection, often accompanying snake's bites.

Standard hemostasis tests are useful for the diagnosis and monitoring of VICC, which is characterized by prolonged PT and aPTT, and elevated D-dimer levels. It is advisable to perform these tests every 6 to 12 hours for continuous monitoring, but POCT can also be valuable in this context. If initial VETs show normal results, patients can be clinically observed without the need for further coagulation studies.[135] In resource-limited settings, the 20-minute whole blood clotting test serves as a primary and sensitive bedside test for detecting coagulopathy when standard laboratory clotting assays are unavailable.[136]

## Hemorrhagic Fever Coagulopathy

Viral hemorrhagic fevers are zoonotic diseases primarily transmitted to humans by vectors such as mosquitoes, ticks, and rodents. These diseases, categorized into seven types by

 

the International Committee on Taxonomy of Viruses, are endemic in certain regions of the world, affecting local populations and travelers alike. The most prevalent is dengue fever, which is primarily distributed in tropical regions. However, other hemorrhagic fevers, such as those caused by the Ebola virus, Marburg virus, and Lassa fever, are frequent occurrences in Africa. Following an incubation period ranging from a few days to several weeks, individuals may experience symptoms including fever and flu-like syndrome.[137] Hemorrhagic fevers are characterized by a significant immune response to the virus with elevated levels of cytokines, dysfunction or deficiency of coagulation factors, increased vascular permeability, complement activation and hemorrhagic manifestations. In severe cases, the disease can progress to multiorgan dysfunction, vasculopathy, and even death. Biologically, patients may exhibit an increase in hematocrit, prolonged PT and aPTT, along with thrombocytopenia, particularly in the early days following admission. The reduction of platelet count is attributed to platelet consumption due to inflammation, sequestration, hypersplenism, and myelosuppression.[138] In contrast to typical viral infections, viral hemorrhagic fevers can result in significant bleeding, and activation of coagulation is closely associated with prognosis.[139] Monitoring the evolution of coagulation times can be beneficial in guiding the correction of coagulation abnormalities and reducing subsequent complications.[140] More than a quarter of patients with hemorrhagic fever will develop complicated coagulopathy and meet the ISTH criteria for DIC.[141]

## Conclusion

Evaluating hemostasis in the ED continues to be challenging for clinicians. It encompasses a thoughtful clinical assessment that includes collection of medical history, accurate physical examination, and inquiries about medication usage and active diseases. In specific cases, laboratory tests become pivotal, but their results can be accurately interpreted only when blood sampling is conducted under appropriate conditions. Clinicians must be mindful of the limitations associated with laboratory testing, emphasizing the need for effective communication with the laboratory. Performing bedside POCT, despite its inherent imprecision and the requirement for trained personnel, offers significant benefits in terms of speed and therapeutic response, particularly in situations such as acute stroke or major bleeding where rapid test results may be crucial to the clinical decision making and cannot be obtained within the 60-minute time frame of standard laboratory tests or in regions with underdeveloped healthcare infrastructure where access to these tests may be limited or even unavailable. However, they should not substitute conventional laboratory tests where these are available and the urgency of the situation does not really require a very short TAT.

**Conflict of Interest**
None declared.

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