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Guidance-Based Appropriateness of Hemostasis Testing in the Acute Setting

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Abstract

In this review, we aim to highlight the extent of inappropriate hemostasis testing and provide practical guidance on how to prevent it. We will focus on the acute setting, including but not limited to the emergency department and intensive care unit. To this end, we will first discuss the significance of inappropriateness, in the general context of laboratory medicine. This includes acknowledging the importance of the phenomenon and attempting to define it. Next, we describe the harmful consequences of inappropriate testing. Finally, we focus on the inappropriate use of hemostasis testing in the acute setting. The second section describes how interventions—in particular, the implementation of guidance for testing—can efficiently reduce inappropriateness. In the third section, we summarize the available recommendations for rational use of hemostasis testing (platelet count, activated partial thromboplastin time, prothrombin time/international normalized ratio, fibrinogen, thrombin time, D-dimer, anti-Xa assay, antithrombin, ADAMTS13 activity, antiheparin-PF4 antibodies, viscoelastometric tests, coagulation factors, and platelet function testing), as supported by guidelines, recommendations, and/or expert opinions. Overall, this review is intended to be a toolkit in the effort to promote the appropriate use of hemostasis testing. Hopefully, the new In Vitro Diagnostic Medical Device Regulation (EU) 2017/746 (IVDR) should help in improving the availability of evidence regarding clinical performance of hemostasis assays.

Keywords
- laboratory tests
- inappropriate
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- IVDR

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Inappropriateness in Laboratory Medicine

The Growing Trend

Laboratory medicine has transformed modern medical patient management.[1] A laboratory test is an accessible, objective, and efficient tool to assess a patient's physiological or pathological state. The use of laboratory tests has grown remarkably in recent years,[2] and this growth has been accompanied by a parallel increase in its misuse. The reasons for this inappropriate use are many, including increased availability of tests and ease of ordering, lack of general knowledge about laboratory tests, lack of understanding or how to interpret the tests, reflex ordering of testing, education and training of residents, use of premade bundles of tests ("panel testing"), asking for analysis instead of formulating a clinical question to be answered by the laboratory, defensive medicine behaviors, or false belief among many clinicians (e.g., we need numbers within the normal range prior to an invasive procedure).[2–5] According to a large, historical meta-analysis, one-third of laboratory tests can be considered inappropriate.[6] More recently, it has been estimated that 60 to 70% of commonly performed tests (including activated partial thromboplastin time [aPTT] and prothrombin time/international normalized ratio [-PT/INR]) may be of questionable clinical relevance.[7] In emergency departments (EDs), and even more so in intensive care units (ICUs), patients are closely monitored as their often critical medical condition can rapidly worsen and may require prompt interventions to avoid unfavorable clinical progression. As a result, acutely ill patients are typically tested several times a day, with extensive laboratory workup compared with other patients, with clinicians often reordering the same tests regardless of the specific half-life of the analyte or any retesting interval recommendation. This testing demand is further intensified by the increasing use of extracorporeal organ support in ICU, particularly renal replacement therapy and mechanical circulatory support such as extracorporeal membrane oxygenation, which are associated with unique hemostatic challenges.[8] These patients are exposed to parenteral antithrombotic agents and experience frequent thrombotic and hemorrhagic complications, which in turn leads to frequent hemostasis-related testing. Consequently, the number of inappropriate laboratory hemostasis-related tests is known to be essentially higher in acute patients.[9]

The Definition

Precisely defining a test as appropriate or not is challenging.[10] In its essence, an appropriate test adds value to the total patient management process. The complexity lies in the definition of the *value*. Value-based approaches to healthcare have focused the definition on the ratio of outcomes produced per money spent.[11] Although value-based healthcare concepts hold great promise for the future of laboratory medicine and healthcare,[12] their use does not alleviate the difficulty of defining appropriateness. Indeed, the *outcomes* must still be defined. It is virtually impossible to quantify the value that a single test result adds to patient care. The value of a test may be as simple as a change in patient management, either to initiate or instead to avoid potential interventions on the patient, as has long been suggested.[13] The outcome can be financial, although with clear shortcomings.[12] Other attempts have been made, such as Lundeberg's proposal to define appropriateness as the predominance of benefits over harms.[14] Nonetheless, in any definition, a scheme of trade-offs between undesirable (e.g., risk) and desirable (e.g., useful clinical information) concepts seems to emerge. Appropriateness seems to lie *within* the process of maintaining this rational balance rather than in the finality of the outcome. In summary, laboratory appropriateness could be defined as the "optimization of human and economic resources, contextually offering the most useful [clinical] information for improving patient outcome and maintaining the highest possible degree of patient safety."[10]

One solution to the definition problem is to use guidelines to define appropriateness: if the test meets the indications, it is appropriate; otherwise, it is not. There are undoubtedly drawbacks to this approach. Guidelines tend to be universal by definition and thus do not capture the variability of particular clinical contexts, an aspect that has been especially highlighted in modern times, as personalized/precision medicine is the new paradigm of care. Evidence-based guidelines are also lacking for specific tests or clinical situations, for which only poorly evidence-based expert opinions can be found. However, this approach has the advantage of being objective and reproducible, two key elements for standardization. In short, if there is no universal and consensual definition of appropriateness, one must be chosen eventually.

The Consequences

Inappropriate testing is detrimental on at least three levels: human (patients and healthcare staff), financial, and environmental.[15] This is sometimes referred to as the triple bottom line or "3P" for People, Profit, and Planet.[16] The form of inappropriateness that most naturally comes to mind is performing tests that should not have been ordered, a phenomenon called overuse. However, its counterpart, underuse, is no less important. Underuse occurs when a test that should be performed is not ordered. It is by nature difficult to detect and its impact on patient care is even more difficult to quantify. Surprisingly, however, a large meta-analysis found that underuse was twice as frequent as overuse,[6] a proportion later found in other hemostasis-focused studies.[17,18] In this section and throughout the rest of this review, we emphasize the importance of keeping in mind that inappropriateness also includes underuse.

First, inappropriateness has human consequences, both for patients and for healthcare workers. A well-described consequence of overtesting-related recurrent phlebotomies is hospital-acquired anemia, a phenomenon particularly prevalent in the ICU and neonatal ICU (NICU), and associated with poorer patient outcomes.[19–22] Furthermore, overtesting mechanically results in more unexpected results—incidentalomas.[23] These incidentalomas cause anxiety for patients, unease for the clinicians, and generally lead to

additional testing, which carries additional costs and risks for the patients and increased workload for healthcare staff. In general, increased staff workload correlates with an increase in medical errors, thereby compromising patient safety. A study[24] estimated that the reduction in inappropriate arterial blood gases alone saved up to 3,736 hours of clinician time in four ICUs over the course of 1 year, showing the impact of inappropriateness on healthcare staff workload. On the other hand, underuse leads to delayed or even missed diagnoses, thus also significantly impacting patient safety,[18] one of the major burdens in health care systems according to a 2024 Organization for Economic Cooperation and Development (OECD) study.[25] A typical example of underuse is the lack of a D-dimer test in patients with a low clinical probability of venous thromboembolism (VTE), which leads to pulmonary angiography being ordered, resulting in unnecessary risks for patients, a high workload for staff and high costs.[26] Finding the right balance between under- and overuse is not always easy. D-dimers are a prime example, as in addition to their aforementioned underuse, it is also known to be overused (typically, in cases where the pretest probability of VTE is high), which increases costs.[27] Missed diagnosis of antiphospholipid syndrome (APS) may be caused by the underuse of lupus anticoagulant testing (LAC), thus exposing the patient to nonprevented thrombotic risk later in life,[10] but testing patients who have a low clinical probability of APS may be considered as overuse.[28] All anticoagulants in clinical use, especially direct oral anticoagulants, interfere with the assays used to detect LAC, including aPTT and the dilute Russell viper venom time (dRVVT).[28,29] Timing of testing in relation to the thrombotic or obstetric complication/during pregnancy is also a very important factor to consider. Testing for LA in the period close to the development of a new thrombosis can lead to false-negative results since elevation in acute phase proteins such as factor VIII and fibrinogen can lead to false-negative results. In contrast, false-positive LAC results can occur due to binding of C-reactive protein to negatively charged phospholipids in the reagent, prolonging phospholipid-dependent clotting tests.[30]

Second, inappropriate testing has a financial burden. Every test has a price, overtesting adds up to unnecessary costs. A recent analysis of 232 million medical records across both Medicare and commercial insurers in the United States found that the overuse of some specific tests (vitamin D, prostate-specific antigen, lipid panel, and hemoglobin A1c) costs the healthcare system $350 million over the course of a single year. Extrapolating their results to all laboratory tests, without accounting for downstream care costs, represented $1.9 to $3.2 billion in unnecessary costs for Medicare in 2019 alone.[31] This is also the case for hemostasis-related tests. Sarkar et al[17] estimated the burden of unnecessary laboratory testing for thrombotic or bleeding disorders at $20,000 per year in a 450-bed U.S. academic center. A recent retrospective analysis of thrombophilia testing in a 355-bed U.S. medical center estimated $150,000 per year in excess costs due to inappropriate testing in the acute care setting alone.[32] Furthermore, the aforementioned studies merely focused on primary costs, which encompass the direct expenses associated with inappropriate use of tests including reagents or calibration costs. It is noteworthy, however, that the actual cost of inappropriateness may be significantly higher. Interventions that monitor economic outcomes should ideally include the "cascade costs" of inappropriateness, such as additional personnel and material costs, prolonged patient stay in the ED or ICU, consequences of incidentalomas in terms of overtesting, overdiagnosis, and overmedication, follow-up costs due to missed diagnosis and treatment, along with environmental consequences (use of plastic tubes, waste material, major use of water, electricity, etc.). However, these consequential costs are notoriously difficult to quantify.

Finally, laboratory medicine has an environmental impact. A large survey of the environmental impact of the Australian healthcare system found that laboratory medicine was responsible for 10% of the environmental impact of healthcare.[33] While the role of laboratory medicine should be evaluated in the broader context of overall global environmental impact,[34] given the rate of inappropriateness, efforts can be made to reduce it. McAlister et al[35] estimated that a coagulation profile was responsible for an average emission of 82 g CO_2 equivalent (CO_2e). In a 936-bed academic center, it was estimated that 77,500 coagulation profiles were ordered annually, representing 6,330 kg CO_2e, or the equivalent of driving 34,000 km in a conventional passenger car.[15] While this example may seem anecdotal at the scale of a single center, it is likely to have a significant impact on the scale of all European laboratories. The exact impact of clinical laboratories is difficult to estimate due to several factors, such as the differences in the type of instrumentation or analytical techniques used to perform the tests, the formulation and origin of reagents, waste management policies, and country-dependent energy source production.[15] For example, a recent study[16] provided estimates three times higher than those previously presented by McAlister et al.[35] However, it is also possible that our current estimates are understated due to the lack of data provided by manufacturing companies.[36] ICUs inevitably contribute more than other units to the environmental impact of hospitals,[37] and laboratory testing plays its part.[38] It is therefore imperative that the environmental impact of inappropriate testing be given greater scrutiny in ICUs in the future.

Collectively, these data show that inappropriate laboratory testing has adverse financial, medical, and environmental consequences (3Ps). Some authors have raised ethical concerns about this issue.[39] One way to begin to curb the trend is to gain a deeper understanding of the underlying causes of inappropriateness, as we will explore further in the following sections.

The Hemostasis Case

Hemostasis tests are among the most commonly performed in clinical laboratories. It is therefore not surprising that a significant number of inappropriate hemostasis tests are ordered. Cadamuro et al[7] evaluated 22,186 aPTT and

36,143 PT/INR tests and reported that up to 60% of those may be of questionable clinical relevance. A similar estimate was made for coagulation testing in the ED: 64% of requests were deemed inappropriate.[40] Sarkar et al[17] reviewed 200 randomly selected cases of bleeding and thrombotic disorders and found that inappropriate testing had a prevalence of 77%. For some tests, such as those composing the thrombophilia screening, the rate of inappropriateness may be even higher. Tientadakul et al[41] examined antithrombin (AT), protein C (PC), and protein S (PS) tests in 503 medical records from a large university hospital in Thailand, showing that 91% of those were inappropriately requested. Another study[32] confirmed this trend in the acute setting of an American academic medical center, reporting an inappropriateness rate of 84% for thrombophilia testing. Another illustrative example of overuse in the acute setting is the use of assays for IgG antibodies against the platelet factor 4/heparin complex (anti-PF4/heparin) in patients with suspected heparin-induced thrombocytopenia (HIT). The 2018 American Society for Hematology guidelines[42] recommend against testing patients with low-probability 4Ts score. In a retrospective analysis of 107 patients who underwent anti-PF4/heparin testing, Jindal et al[43] demonstrated that 51 patients (48%) received a low-probability score, indicating that approximately half of the requests were inappropriate (none exhibited a strongly positive ELISA test result). In a similar study conducted by Beauverd et al,[44] the number of patients tested for anti-PF4/heparin, although labeled with a low-probability score, was as high as 73%, none being diagnosed with HIT. Publications from Canada, France, and Switzerland indicate that a small percentage (1.5–9%) of patients with "low HIT probability" with a 4T score of 3 have indeed HIT. Considering the consequences of a missed HIT diagnosis, the authors consider only 4T scores of 0 to 2 as a reason not to test for anti-PF4/heparin antibodies.[45] D-dimer is also a commonly ordered test in the acute setting, with several reports indicating overuse.[46–48]

Collectively, those studies suggest that there is a high frequency of inappropriate ordering of hemostasis tests, particularly in the acute care setting. It is possible that we are seeing only the tip of the "iceberg of inappropriateness in hemostasis testing."[10] The authors' experience suggests that less well-studied tests such as anti-Xa assay to measure anticoagulants, ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs 13), TT, fibrinogen, platelet function tests, AT, or factor V levels may be overprescribed in some centers, suggesting that the reality of inappropriate hemostasis testing may be much larger than commonly appreciated.[49,50] It is therefore crucial to focus on strategies to reduce their inappropriate use.

Guidance-Based Appropriateness of Hemostasis Testing H1

The Solutions

Education and increasing the awareness of inappropriateness and its downstream consequences have led laboratory specialists to develop interventions. An intervention can be defined as any action taken to reduce the inappropriate use of laboratory resources, in a process often referred to as laboratory demand management.[51] There are numerous examples of interventions, which have been reviewed elsewhere.[51–61] Interventions with common methodology have been grouped together into distinct categories, namely, education and/or guidance (sometimes considered as a single strategy), audit and feedback, computerized physician order entry (CPOE) coupled with demand management tools, gatekeeping, multifaceted intervention when at least two different strategies are used together, and a recently coined category of artificial intelligence/machine learning-based algorithms.[9] Each type of intervention is characterized by its respective ease of implementation, its efficiency, its effectiveness over time, and its resource requirements (either temporal or economical). For example, multifaceted interventions have a higher efficiency and persistence over time than educational interventions, but they are more difficult to implement and sustain.[9] The bottom line is that most interventions are effective and feasible overall, although some more than others, and most importantly that they are safe for the patients.[9,62]

The Examples

Fortunately, there are many examples of effective interventions to reduce the inappropriateness of hemostasis testing in the acute care setting. A comprehensive review of interventions implemented in ICUs to reduce the rate of inappropriate testing[9] found a mean reduction in inappropriate hemostasis-related tests of 41% (range: 8–64%) in the post-intervention period compared with the preintervention period. In these interventions, one[63] specifically tested the effectiveness of a guideline to reduce unnecessary coagulation tests (PT/INR, aPTT, and fibrinogen) in an ICU. The authors found that the implementation of locally established guidance resulted in a 64% reduction in coagulation tests, and estimated cost savings of nearly AUS$100,000 per year for a 23-bed ICU; extrapolated to all ICUs in Australia and New Zealand, this represents savings of more than AUS$3.8 million in 1 year (as of 2014).

Illustrative examples can be found in the literature regarding anti-PF4/heparin testing in patients suspected of HIT. Cadamuro et al[64] observed that simply requiring clinicians to utilize the 4T score when ordering an anti-PF4/heparin immunoassay could effectively reduce the overuse of this test. Similarly, a study[65] that developed a clinical decision support tool, comprising a 4T score calculator and platelet count versus time graph, was able to result in the discontinuation of 25% of tests for clinicians ordering anti-PF4/heparin immunoassays. Even a relatively straightforward intervention, such as the introduction of an automatic electronic alert in the CPOE system, was shown to yield a notable reduction in the ordering of inappropriate anti-PF4/heparin tests.[66] A recent scoping review[67] on quality improvement interventions on HIT testing appropriateness retrieved 30 studies, identifying five main directions to improve HIT testing: increasing HIT recognition, reducing HIT incidence, reducing HIT overdiagnosis, promoting safer HIT management, and creating HIT task forces.

Specific, individualized interventions have also yielded substantial improvements in reducing inappropriate hemostasis testing. A study[68] of patients admitted to the emergency general surgery department of a 922-bed facility showed a 17% reduction in the ordering of coagulation tests (PT/INR and aPTT) on admission after an education and guideline-based intervention—while this study referred to the 2008 British Committee for Standards in Haematology guidelines for preoperative bleeding risk assessment,[69] it is here pertinent to advise the reader that the British Society for Haematology (BSH) guidelines have recently undergone an update,[70] and now advise against routine coagulation screening prior to invasive procedures. In another multifaceted intervention, Tawadrous et al[71] uncoupled INR and aPTT testing and provided education and reminders through the CPOE system. The intervention resulted in a 54% decrease in the total number of tests performed and an estimated savings of CAN$163,000. This number is also found in another multifaceted plan-do-study-act (PDSA)-based intervention[72] for coagulation testing in the ED. In another study, an original strategy was used. Kalsi et al[73] designed a two-part intervention: in the first part, they used an educational strategy; in the second, they physically removed the tubes needed for coagulation testing from the bedside trolleys in the ED. Interestingly, there was no change in the ordering of coagulation tests after the educational intervention. However, the rate of inappropriate coagulation testing dropped from 74 to 53% after the simple removal of tubes from the ED trolleys. In addition to highlighting the creativity of some interventions, this example illustrates how simple interventions can yield significant results.

These studies show that interventions are effective in reducing inappropriate hemostasis testing and result in cost savings, but reducing inappropriate hemostasis testing may also benefit the environment. Recently, Pilowsky et al[24] conducted a massive multifaceted intervention (education, audit, and feedback strategies) in the ICUs of four Australian centers over a 12-month period, analyzing 460,258 tests from a total of 22,210 patients. By breaking down the tests, coagulation testing alone accounted for 480 kg of CO_2e emissions and AUS$120,000 saved; the intervention resulted in a total reduction of 1.8 tons CO_2e emissions and saved nearly AUS$1 million.

While some interventions, as previously mentioned, directly address the inappropriate use of laboratory tests, others are designed to mitigate their unfavorable consequences. For example, Siegal et al[22] showed that the transition from standard to small-volume tubes in the ICU resulted in a reduction in the number of transfused red blood cell units per ICU patient-day without any impact on laboratory testing. Furthermore, a recent intensive care medicine rapid practice guideline panel has issued a "strong recommendation for the use of small-volume sample collection tubes in adult ICUs."[74]

In conclusion, effective interventions can be designed to reduce inappropriate hemostasis testing. Such interventions reduce the rate of inappropriate testing, save costs, and reduce the environmental impact of laboratory medicine.

The Guidance

One of the most commonly used strategies is guidance-based interventions. This approach provides clinicians with precise indications for testing. In general, guidelines or guidance aims to define the "what, who, and when" of testing; inspired by the Choosing Wisely initiative,[75] they amount to answering the "6-Rs" for each test, that is, the choosing of (1) the right test, with (2) the right method, at (3) the right time, for (4) the right patient, at (5) the right cost, and for obtaining (6) the right outcome.[76] In the aforementioned review of 44 interventions conducted to reduce inappropriate testing in the ICU, 22 mentioned a guidance-based strategy.[9] Surprisingly, when examining the documents used in the interventions, none referred to international or even national guidelines. Instead, in all cases, guidance was based on local expert consensus. Closer examination of different guidance revealed discrepancies (see ►Table 1 for an example regarding coagulation testing), showing (1) that we need more evidence and (2) that standardization in the context of guidance-based interventions—and more generally speaking in the ordering of laboratory tests—is certainly needed.[77–81]

There is evidence in the literature that compliance with recommended hemostasis testing is low.[82] This is mainly due to the strong beliefs of some clinicians that (1) PT and aPTT can assess hemostasis and predict the bleeding risk in patients undergoing invasive procedures; (2) abnormal laboratory test results indicate the increased risk of significant bleeding after a procedure; (3) interventions such as plasma transfusion can correct abnormal PT and/or aPTT, reducing the bleeding risk; (4) normal platelet count reassures on the low/no risk of bleeding in all patients, while platelet transfusion will modify and reduce bleeding risk in all thrombocytopenic patients; (5) risks of transfusion will not exceed the benefits of transfusion. Unfortunately, those beliefs have been continued to varying degrees in clinical practice, promoting inappropriate hemostasis testing and trying to achieve specific laboratory thresholds for prophylactic transfusions, despite generally low levels of supporting evidence.[70,83]

In a survey of 81 Korean laboratories, only 13 reported following the correct indication for anti-factor Xa testing in low-molecular-weight heparin (LMWH) monitoring.[84] Anderson et al[85] recently showed that only 15% of inpatient thrombophilia testing met the 2023 American Society for Hematology guidelines[86] criteria for thrombophilia screening. There are many barriers to guideline implementation and compliance, including lack of awareness or accessibility of the guideline, lack of agreement, lack of practicality (i.e., when the guidelines are not appropriate for real-world practice), 'environmental' (i.e., institutional, political, cultural, or social) factors, or simply time constraints.[87–90] In some cases, the guideline itself is a problem from a laboratory perspective. Clinical practice guidelines are often formulated for specific clinical scenarios in which laboratory medicine is not the primary focus but plays a key role. In such cases, failure to include laboratory specialists in the development process of the guidelines or care pathways may result in establishing inappropriate testing recommendations.[87]

Table 1 Discrepancies in guidance for the same test (coagulation profile) between studies in ICUs

Kumwilaisak et al[78]	Not routine
Dhannai et al[79]	Only as required (order individual tests)
Kotecha et al[80]	Bleeding, coagulopathy, on anticoagulation, planned procedure
Musca et al[63]	At admission (if not already done) Significant bleeding, coagulopathy, new thrombocytopenia ($< 50 \times 10^9$/L), liver failure, or disseminated intravascular coagulation (DIC) (once and then daily if abnormal) If warfarin therapy and isolated high INR (> 1.3): INR only, daily, or less when the patient is improving If heparin therapy and isolated high aPTT: aPTT only, as per heparin protocol, or daily or less if patient improving; If the coagulation profile is abnormal but none of the above: consider ordering a coagulation profile second daily or less if the patient improving
Prat et al[81]	Upon admission to ICU When DIC or hepatic failure During ICU stay once or two times a week (if heparin treatment once a day until aPTT ok *(sic)* and after 2–3 times a week)

Abbreviations: aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; ICU, intensive care unit; INR, international normalized ratio.

Notes: When inspecting guidance provided in the methodology of interventions aimed at reducing inappropriate testing in ICUs, none were international, standardized guidelines but instead locally established guidance. Comparing these guidance highlights discrepancies (below, for coagulation testing). Each line of this table is a guidance from one of these studies. The coagulation profile here encompasses international normalized ratio/prothrombin time, activated partial thromboplastin time, and fibrinogen testing.

The Future

A new type of intervention is now using artificial intelligence (AI) to help reduce inappropriate testing.[91] In 2013, Cismondi et al[92] used a predictive tool, "fuzzy modeling," to evaluate unnecessary testing in patients with gastrointestinal bleeding in the MIMIC-II ICU database. The analysis showed that aPTT, PT, and fibrinogen tests were irrelevant in 43%, 57%, and 84% of the cases, respectively, pointing to opportunities for improvement in resorting to laboratory testing. One could imagine that the help of AI tools combined with CPOE systems could create a kind of 'intelligent' computerized clinical decision support[93] that would help clinicians decide which tests to order based on clinical data, patient's medical history, and previous test results. Indeed, the very essence of laboratory testing is to provide clinicians with information. If the test adds clinically useful information, it can be considered appropriate. Predicting the value that a test will add is therefore a key argument in test ordering practice. Lee and Maslove[94] have used information theory principles to examine the novelty of information that daily repetition of certain tests in ICU patients carries. Surprisingly, they concluded that platelet count was one of the tests with the least novel information on days 2 and 3 after ICU admission. The idea that AI could allow us to avoid performing certain tests by their virtual prediction is not science fiction. In 2020, a team developed a deep learning algorithm that was able to reduce the total number of laboratory tests used in ICU patients by 20%, with 98% accuracy in predicting abnormal results.[95] Interestingly, platelet count was again one of the most commonly omitted tests with this tool. AI can also provide additionally useful information. For example, Fang et al[96] used backpropagation neural networks (BPNNs) that were trained and validated with training and testing datasets to identify clotted specimens. By combining the results of five basic coagulation tests (aPTT, PT, fibrinogen, thrombin time [TT], and D-dimer) with the patient's age, the system was able to identify clotted samples with 97% accuracy, preventing unreliable results from being provided to requesting physicians.

Viewing laboratory tests as information, AI can also add value to tests already performed. In fact, there is a growing body of evidence showing that the aggregation of data coming from multiple tests (i.e., routine "bundle" testing) can accumulate into new information. This is actually not so different from what human clinicians and laboratory specialists do with test results: rather than viewing tests as separate "information givers" one at a time, they "aggregate" the information provided by multiple tests into a coherent interpretation—a diagnosis. However, with the help of AI (e.g., unsupervised algorithms), this could be brought to another scale and with a fine degree of optimization, potentially leading to a reduction in a significant number of tests.

It should be noted that AI tools have important drawbacks and present ethical challenges, notably the inherent "black box design" of unsupervised algorithms, global lack of real-world data both in terms of quantity and quality, lack of interreproducibility between different sets of data (e.g., training and real-world data), and data privacy.[9,12,97] Collectively, AI, while not yet mature, will certainly be a valuable tool in the future to assist clinicians and laboratory specialists in their quest to improve appropriate laboratory testing.[98]

There is a growing interest in improving the appropriate use of laboratory tests. In a survey conducted in nine European countries, the vast majority of laboratory specialists and clinicians felt that measures to ensure the appropriate use of tests were necessary, and all respondents' clinicians were interested in advice/information on their indication.[99] Close collaboration between clinicians and specialists in laboratory medicine will be essential to

improve the use of laboratory testing. Recommendations or automated implementation of test profiles or laboratory diagnostic pathways, (i.e., to trigger tests based on symptoms or diagnostic hypotheses as is already the case for anemia or flow cytometry in hematology), must be based on current evidence.[12] The new In Vitro Diagnostic Medical Device Regulation (EU) 2017/746 (IVDR) requires clinical evidence, which is based on the intended use (indication) and risk class (B or C for most of the hemostasis assays).[100] We, therefore, hope that this will lead to more evidence for the correct use of hemostasis tests.

Recommendations for the Rational Use of Hemostasis Tests in the Acute Setting

The implementation of guidance-based interventions represents an effective strategy to implement in the acute care setting. However, the selection of guidelines upon which these interventions are based is critical. It is not uncommon for such interventions to make no mention of guidelines published by expert committees or national/international specialty societies. In this section, we have attempted to summarize the current guidance for commonly ordered hemostasis tests in the acute and inpatient settings, namely platelet count, aPTT, PT/INR, fibrinogen, TT, D-dimer, anti-Xa assay, AT, ADAMTS13 activity, antiheparin-PF4 antibodies, viscoelastometric tests, factor V levels and platelet function testing (►Table 2). Additionally, we present key guidance or guideline categorized by specific clinical situations (►Table 3).

A common cause of overuse is inappropriate retesting. An effective method of limiting retesting is the implementation of a minimum retesting interval (MRI),[101] which indicates the time window below which repeating the same test in the same patient is likely to be inappropriate in the absence of any significant clinical change or therapeutic intervention, e.g., transfusion. There are already valuable examples of how the use of this approach may substantially reduce the burden of potentially inappropriate retesting, such as that presented in Lippi et al,[102] where a CPOE alert system encompassing pop-up alerts based on retesting interval for 15 laboratory tests yielded a reduction of nearly 13% of the overall cost of laboratory testing. In the absence of any kind of therapeutics, either drug or transfusion, it is also inappropriate to retest the same patient below the half-life of the analyte or drug being tested (when applicable), as the effect measured is unlikely to reflect the real change in the analyte dynamics. For that reason, we have added a column to the table referring to half-life and existing MRI recommendations.

In light of this guidance, we provide below explicit examples of inappropriate (and/or debated) use of standard hemostasis assays in various clinical settings. In general, when considering clotting times, it is preferable to use PT on its own rather than in combination with aPTT, with the exception of cases where the aim is to investigate bleeding that may be caused by inherited or acquired deficiencies in factors VIII, IX, and XI. In such instances, a suitable reagent must be used that is sensitive enough to detect these deficiencies. There are several reasons to preferentially rely on PT over aPTT, given that the latter is subject to numerous drawbacks. These include a high degree of sensitivity to the preanalytical phase,[103] particularly if collected through an inserted vascular line or catheter. Additionally, aPTT is often prolonged for reasons that have no clinical impact. A shortened aPTT, however, may indicate an inflammatory state that accelerates coagulation; nevertheless, the clinical utility of such a finding remains uncertain.[104] Therefore, PT should be the preferred method for detecting acquired coagulopathies, with the exception of the rare condition of acquired hemophilia (auto-antibodies to FVIII) and exceptional auto-antibodies to FIX and FXI.[105] Additionally, in cases of anticoagulation with a vitamin K antagonist, during a bleeding event, or prior to an invasive procedure, aPTT may indicate the rare variant of FIX that renders patients hypersensitive to vitamin K antagonists (VKA), which would otherwise be undetected through INR.[106,107] It is imperative that the aPTT be determined prior to the commencement of any anticoagulant treatment. An extended aPTT may indicate the presence of a lupus anticoagulant, which has a clinical impact. This may be the case in instances where there is a suspected catastrophic APS.[108] In such instances, when there is an acute thrombotic event, parenteral anticoagulation is switched to the oral route, VKA should be preferred over direct oral anticoagulants (DOACs).[109,110] In the event that a basal aPTT is conducted at the time of admission or at the onset of an acute intercurrent illness and yields a normal result, retesting of aPTT is not an efficacious course of action (although it may be employed for unfractionated heparin (UFH) monitoring, for those who still utilize it, either alone or in conjunction with an anti-Xa assay).

Liver Disease

The liver is the main organ for synthetis of the majority of coagulation factors as well as for naturally occurring coagulation inhibitors such as AT, PC, or PS. Liver disease leads to a reduction in the synthesis of coagulation factors, resulting in prolonged PT as well aPTT in severe cases but also in a reduction of anticoagulants. Similarly, hypersplenism, induced thrombocytopenia is compensated by an increase in endothelium-derived von Willebrand factor (VWF), which enhances platelet function.[111] Consequently, liver diseases contribute to an rebalanced hemostatic system, resulting in a normocoagulable or hypercoagulable state that cannot be detected by conventional coagulation tests.[112,113] In this context, prolonged PT and thrombocytopenia are not reliable predictors of bleeding risk, and current guidelines do not recommend the use of blood components (fresh frozen plasma, prothrombin complex, fibrinogen) to correct those abnormalities for management of periprocedural bleeding.[114,115] The misconception that conventional coagulation tests indicate a hypocoagulable state in patients with cirrhosis is reinforced by the frequent hemorrhagic complications associated with this condition. Hemorrhagic events in patients with liver disease or cirrhosis are primarily due to mechanical causes in which the hemostatic state has little influence.[116] Transfusion of blood components to correct the alleged hemostatic defect is not only ineffective, but may also

Table 2 Suggested guidance or guidelines for hemostasis tests in the acute setting

Test	Half-life or time of turn-over	Main indication(s)/ intended use	Key messages	Minimal retesting interval	Key references
Platelet count	4–6 d	Detection of thrombocytopenia in ICU	Many mechanisms of thrombocytopenia. Included in SIC scoring system to categorize early-phase DIC in sepsis Screening for overt DIC on the day of ICU admission was associated with lower mortality, and the association became stronger if the screening was repeated 2 days later, suggesting that DIC screening by itself might lead to improved outcomes (Umemura et al)[143] Use SIC score to detect the earlier phase of DIC (Iba et al)[144]	Daily Exception, suspicion of HIT: - Systematic platelet count before initiation of treatment by UFH/LMWH - For patients at intermediate risk of HIT, it is proposed to monitor platelet counts once to twice a week from days 4 to 14 of treatment, and then once a week for 1 mo if heparin therapy is continued - For patients at high risk of HIT, it is proposed to monitor platelet counts two to three times a week from days 4 to 14 of treatment, and then once a week for 1 mo if heparin therapy is continued	Thachil and Warkentin[145] Greinacher and Selleng[146] Greinacher[147] Cuker et al[42] Gruel et al[148] Iba et al[144] Iba et al[121] Wada et al[149] Thonon et al[49]
		Active bleeding	Monitoring is indicated to detect the threshold for platelet transfusion even if these thresholds are not validated. ESAIC guidelines recommend a goal-directed transfusion strategy (based on Hb and/or physiological red blood cell transfusion triggers, coagulation factor substitution, and platelet transfusion triggers)	According to clinical evolution (Kietaibl et al)[50]	Lang and Croal. National minimum retesting interval in pathology 2021[101] Spahn et al[151] Lippi et al[152] Lang et al[101]
aPTT	N/A	Monitoring of UFH	Use a weight-adjusted nomogram with timely laboratory monitoring Anti-Xa assay is often preferred to aPTT for this indication	Check anti-Xa UFH levels 6 h after any change in dose, or at least once per day	Lippi et al[153] Raschke et al[154] Smith and Wheeler[155] Baker et al[156] Gouin-Thibault et al[157] Thonon et al[49]
		Follow-up of DIC	No test “In bleeding patients with DIC and prolonged PT and aPTT, administration of FFP may be useful. It should not, however, be instituted based on laboratory tests alone but should be considered in those with active bleeding and in those requiring an invasive procedure. (Grade C, Level IV).” (Levi et al)[158] However, aPTT is not mentioned in ISTH guidelines (Iba et al)[121,144] DIC is a highly dynamic situation: “it is important to repeat the tests to monitor the dynamic changes on the basis of laboratory results and clinical observations” (Wada et al)[149]	No retest	Wada et al[149] Thonon et al[49]

(*Continued*)

Table 2 (*Continued*)

Test	Half-life or time of turn-over	Main indication(s)/ intended use	Key messages	Minimal retesting interval	Key references
		Suspected bleeding disorder: - Inherited: clotting factor deficiency (intrinsic pathway), von Willebrand disease - Acquired: acquired factor inhibitors (e.g., autoantibodies to factor VIII aka "acquired hemophilia"), anticoagulants	aPTT is sensitive neither to some von Willebrand factor defects nor to platelet function defects and factor VII and factor XIII deficiencies	Confirmation required along with specific testing of coagulation factors	Lee[159] Thonon et al[49] Casini et al[160]
PT/INR	N/A	Assessment of the anticoagulant effect of VKAs in case of severe bleeding or before an invasive procedure	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 (Kuramatsu et al).[161] It is also recommended to check the INR within 30 min at 6 to 8 h and 24 h after antagonization, to decide on further administration of PCC (Schwebach et al).[162] Obtaining INR results quickly is crucial in certain conditions for patients taking VKAs. Stroke management guidelines recommend thrombolytic therapy within 4.5 h after stroke onset for patients on warfarin therapy only if their INR is below 1.7 (Powers et al).[163] 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.		Bonhomme et al[164] Association of Anaesthetists of Great Britain and Ireland (Anesthesia 2010)[165] Advisory panel guidance on minimum retesting intervals for laboratory tests[166] Pernod et al[167] Thonon et al[49]
		Diagnosis and follow-up of DIC (included in SIC scoring system)	DIC is a highly dynamic situation: "it is important to repeat the tests to monitor the dynamic changes on the basis of laboratory results and clinical observations" (Wada et al).[149] Included in SIC scoring system to categorize early phase DIC in sepsis "Screening for overt DIC on the day of ICU admission was associated with lower mortality, and the association became stronger if the screening was repeated 2 d later, suggesting that DIC screening by itself might lead to improved outcomes" (Umemura et al)[143]	If SIC scoring system is positive, daily (DIC)	Umemura et al[143] Iba et al[144] Iba et al[121] Wada et al[149] Thonon et al[49]
		Major bleeding	"We recommend that monitoring and measures to support coagulation be initiated immediately upon hospital admission (Grade 1B)" (Rossaint et al)[126] "We recommend that resuscitation measures be continued using a goal-directed strategy, guided by standard laboratory coagulation values and/or VEM (Grade 1B)." (Rossaint et al)[126] "If an FFP-based coagulation resuscitation strategy is	According to the clinical evolution (Kietaibl et al)[150]	Rossaint et al[126] Lang and Croal. National minimum retesting interval in pathology 2021[101] Thonon et al[49] Kietaibl et al[150] Lang et al[101]

Table 2 (*Continued*)

Test	Half-life or time of turn-over	Main indication(s)/ intended use	Key messages	Minimal retesting interval	Key references
			used, we recommend that further use of FFP be guided by standard laboratory coagulation screening parameters (PT and/or aPTT > 1.5 times normal and/ or viscoelastometric evidence of a coagulation factor deficiency) (Grade 1C)" (Rossaint et al),[126] except in cirrhotic patients (Lawrence and Siau[168] ESAIC guidelines recommend a goal-directed transfusion strategy (based on Hb and/or physiological red blood cell transfusion triggers, coagulation factor substitution and platelet transfusion triggers)		
		Suspected bleeding disorder: - Inherited: clotting factor deficiency (extrinsic pathway) - Acquired: acquired factor inhibitors, anticoagulants	PT is not sensitive to von Willebrand factor defects, platelet function disorders, factors VIII, IX, XI, and XIII deficiencies	Confirmation required along with specific testing of coagulation factors	Lee[159] Thonon et al[49] Casini et al[160]
TT		Exclusion of anti-IIa anticoagulant	Many variables affecting TT, lack of standardization between laboratories Thrombin time should not be used to assess dabigatran concentrations in the normal therapeutic range		Lippi and Favaloro[169] Lessire et al[170]
Fibrinogen		Major bleeding	"We recommend early and repeated monitoring of hemostasis, using a traditional laboratory determination such as PT/INR, Clauss fibrinogen level and platelet count and/or POC PT/INR and/or a viscoelastometric method (Grade 1C)." (Rossaint et al)[126]	According to the clinical presentation and evolution (Kietaibl et al)[150]	Rossaint et al[126] Kietaibl et al[150]
D-dimer	6–8 h	Diagnosis of DIC	D-dimer cut-off should be adapted to the reagent "Screening for overt DIC on the day of ICU admission was associated with lower mortality, and the association became stronger if the screening was repeated 2 d later, suggesting that DIC screening by itself might lead to improved outcomes" (Umemura et al)[143] DIC is a highly dynamic situation: "it is important to repeat the tests to monitor the dynamic changes on the basis of laboratory results and clinical observations" (Wada et al)[149]	Daily if SIC scoring system is positive	Wauthier et al[171] Suzuki et al[172] Wada et al[149] Thonon et al[49]
		Exclusion of venous thromboembolism	Use age-adjusted D-dimer cut-offs for diagnosing acute episodes of venous thromboembolism	No retest	Favaloro et al[173]

(*Continued*)

Table 2 (*Continued*)

Test	Half-life or time of turn-over	Main indication(s)/ intended use	Key messages	Minimal retesting interval	Key references
Anti-Xa assay	UFH: The half-life of UFH is dose-dependent, ranging from 60 to 90 min at usual IV doses	Monitoring of UFH	UFH: Use a weight-adjusted nomogram with timely laboratory monitoring (to reach more rapidly the therapeutic range, to reduce the number of dose adjustments and to reduce the number of thrombotic events)	According to a nomogram	Baker et al[156] Gouin-Thibault et al[157] Thonon et al[49]
	LMWH: - Tinzaparin, dalteparin, nadroparin: 4–6 h - Enoxaparin: 5–7 h	To detect an accumulation/ overdosage of LMWH (at peak)	The LMWHs vary in their physicochemical properties, the anti-Xa:anti-IIa ratio	Only in case of persistent bleeding	Gouin-Thibault et al[174] Thonon et al[49]
	Anti-Xa DOACs (7–17 h: interindividual variability)	Measuring of DOAC levels (with dedicated calibration) in case of bleeding, antidote administration, invasive procedure	Should be measured within 30 min in case of: - Bleeding - Urgent invasive procedure - Thrombolysis On-therapy range is available at trough and peak (Douxfils et al)[175]	Only in case of persistent bleeding	Douxfils et al[175] Baker et al[156] Levy et al[176] Berge et al[177] Thonon et al[49]
AT	Several days: 66.2 h ± 1.2 according to Knot et al)[178]	Diagnosis of DIC	Disagreement between recommendations. AT is included in the revised diagnostic criteria for DIC from the Japanese Society on Thrombosis and Hemostasis (Wada et al)[179] but not in the ISTH overt DIC scoring system (Iba et al)[121]	No retest	Iba et al[121] Wada et al[179] Thonon et al[49]
		"Heparin resistance" or dampened response to UFH	Heparin resistance could be defined as UFH failure to achieve a specified anticoagulation level despite the use of what is considered to be an adequate dose of heparin There is no consensus on its definition and therefore on the reported incidence Its reality is even challenged[180] Acquired antithrombin deficiency (frequent in ICU due to sepsis, DIC, ECMO, or liver disease) can cause a dampened response to UFH, but there is no clinical benefit demonstrated when antithrombin is administered (Mansour et al)[50] In patients with large volume blood loss, although AT replacement can be considered based on levels below the normal reference range, data supporting this management strategy are needed" (Helms et al)[181] illustrating disagreement between ISTH and Extracorporeal Life Support Organization (ELSO) guidelines "Antithrombin levels [are] not significantly associated with heparin responsiveness" during venoarterial ECMO (Mansour et al)[50]	No retest (as there is no clinical benefit demonstrated when antithrombin is administered)	Van Cott et al[182] Levy et al[183] Gouin-Thibault et al[180] Thonon et al[49] Helms et al[181] McMichael et al[184]

Table 2 (*Continued*)

Test	Half-life or time of turn-over	Main indication(s)/ intended use	Key messages	Minimal retesting interval	Key references
ADAMTS13	A median half-life of 130 h was demonstrated, ranging between 82.6 and 189.5 h according to Taylor et al[185]	Diagnosis and follow-up of thrombotic thrombocytopenic purpura	Use clinical score (French or Plasmic score) to predict severe ADAMTS13 deficiency (except in specific clinical conditions like obstetric or pediatric populations)	Acute stage: diagnosis once then weekly after plasma exchange (PEX) Long-term follow-up: every 3 mo	Scully et al[186] Zheng et al[187] Graça et al[188] Coppo et al[189] Scully et al[186] Thonon et al[49]
Antiheparin-PF4 antibodies immunoassays	Undetectable levels at a median of 50–85 d after the HIT acute stage	Diagnosis of HIT if pre-test probability (e.g., 4T score) is not low	Limitations of 4T score in ICU Negative predictive value of a low 4T score (91–98.5%, only 74% of the agreement for the fourth T (other) (Crowther et al)[45] (Marchetti et al)[190]	No retest If pre-test probability is high and IA negative, a platelet activation assay may be appropriate	Cuker et al[42] Gruel et al[148] Warkentin et al[191] Crowther et al[45] Linkins et al[192] Arachchillage et al[193] Thonon et al[49]
Viscoelastometric testing (TEG, ROTEM, QUANTRA, etc.)	N/A	Might be considered to guide transfusion in case of massive bleeding (during cardiac surgery, liver disease, obstetrical bleeding and hyperfibrinolysis, etc.)	"We recommend the early and repeated monitoring of hemostasis, using a traditional laboratory determination such as PT/INR, Clauss fibrinogen level, and platelet count and/or POC PT/INR and/or a viscoelastometric method (Grade 1C)." (Rossaint et al)[126] In cases of severe (poly)trauma, there is a significant and widespread release of tPA from damaged endothelial cells throughout the body, primarily due to severe hypoperfusion and other factors. In some situations, the amount of released tPA is so substantial that it overwhelms the available levels of PAI-1. This results in an increase in free circulating plasmin, which is capable of degrading fibrinogen and other plasma proteins. (Gall et al)[194]; (Walsh et al)[195] POCTs (TEG, ROTEM) are faster but relatively insensitive for accurate diagnosis of increased fibrinolytic activation, Thus, they underestimate the incidence and severity of fibrinolytic activation in trauma (Raza et al)[196] (Gall and Davenport).[197] However, be aware of the following drawbacks of these tests: significant variability, making them non-interchangeable; lower analytical and clinical performance; higher costs compared with central laboratory devices; insufficient staff training, increasing the risk of errors; lack of systematic checks for preanalytical errors, such as hemolysis and contamination; the need for predefined algorithms and decision-making thresholds; many POC devices contribute to environmental waste due to the use of unsustainable materials. Implementation of viscoelastometric testing into an	According to the clinical situation and the treatment algorithm	Hartmann et al[199] Mansour et al[119] Thonon et al[49] Rossaint et al[126] Kietaibl et al[150]

(*Continued*)

Table 2 (*Continued*)

Test	Half-life or time of turn-over	Main indication(s)/ intended use	Key messages	Minimal retesting interval	Key references
			integrated transfusion algorithm during cardiac surgery, liver transplantation, or acute severe trauma, can lead to: - Reduced red blood cell transfusions - Reduced platelet transfusions - Reduction in major postsurgical bleeding Be aware of the limitations of VETs - Insensitivity for detecting von Willebrand factor and minor/moderate fibrinolytic activity - Natural anticoagulants - No results of interchangeability between instruments technologies Clinical evidence of the utility of VHAs largely remains to be proven through randomized clinical trials, with clinically relevant outcomes, and compared with rapid panel hemostasis testing[198]		
Factor V	36 h according to Mannucci et al[200]	In cases of acute liver failure, 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. A factor V level below 20% for patients under 30 y of age, and below 30% for patients aged 30 or older, is a severity criterion indicating the need for liver transplantation. Unfortunately, factor V 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	No retest	Müller et al[201] Goel et al[202] Thonon et al[49]
Platelet function testing	Clopidogrel: 6–8 h Prasugrel: 7 h (2–15 h)	"P2Y12 inhibitor monitoring to shorten the time window to surgery following P2Y12 inhibitor discontinuation. (Class IIa, Level B)" (Frelinger et al)[203]	Variability in platelet reactivity recovery time for clopidogrel, prasugrel and ticagrelor There are different platelet function tests that are not interchangeable Several preanalytical constraints should be managed	No retest	Frelinger et al[203] Godier et al[204] Valgimigli et al[205] Ferraris et al[206]

Abbreviations: aPTT, activated partial thromboplastin time; AT, antithrombin; d, days; DIC, disseminated intravascular coagulation; DOACs, direct oral anticoagulants; ESAIC, European Society of Anaesthesiology and Intensive Care; FFP, fresh frozen plasma; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; mo, months; PAI-1, plasminogen activator inhibitor-1; POC, point-of-care; POCT, point-of-care testing; PT, prothrombin time; SIC, sepsis-induced coagulopathy; tPA, tissue plasminogen activator; TT, thrombin time; UFH, unfractionated heparin; VEM, viscoelastometric monitoring; VKA, vitamin K antagonists.
Notes: Note that the level of evidence underpinning the use of hemostasis tests in the acute setting is highly variable according to the assay. The reader should thus refer to the key references.

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Table 3 Suggested guidance for the use of hemostasis tests in the acute setting, for some clinical scenarios

Indication	Diagnosis	Follow-up	References
SIC/DIC	There is no gold standard for the diagnosis of DIC, and no single test that is, by itself, capable of accurately diagnosing DIC (ISTH/SCC 2013) SIC score is diagnosed based on platelet count, PT, and SOFA score (ISTH 2023) DIC diagnosis should include platelet count, D-dimer, fibrinogen level and PT. The utility of fibrin monomers and AT is still debated (proposed and validated by JSTH but not included in ISTH score)	According to the clinical presentation and evolution (at least daily)	BCSH 2009 guidelines (updated 2012)[158] ISTH 2023 communication[121] JSTH 2016 diagnostic criteria[207] SISET 2012 guidelines[208] ISTH/SCC 2013 harmonization guidance[149] Aota et al[209]
Cirrhosis	No test recommended (thrombomodulin-modified thrombin generation: for research use only)	No test recommended	Tripodi et al[120]
HIT	*Platelet count* Systematic assessment of platelet count before initiation of treatment by UFH/LMWH For patients at intermediate risk of HIT, it is proposed to monitor platelet count once to twice a week from days 4 to 14 of treatment, and then once a week for one month if heparin therapy is continued For patients at high risk of HIT, it is proposed to monitor platelet count two to three times a week from days 4 to 14 of treatment, and then once a week for one month if heparin therapy is continued. *Antiheparin-PF4 antibodies* Antiheparin-PF4 antibodies immunoassays if pre-test probability (e.g., 4T score) is not low *Functional test* If the pre-test probability is intermediate or high and a significant titer of antiheparin-PF4 antibodies is detected, a functional test should be performed. If pre-test probability is high and immunoassay is negative, a functional test may be appropriate	For patients at intermediate risk of HIT, it is proposed to monitor platelet count once to twice a week from days 4 to 14 of treatment, and then once a week for 1 mo if heparin therapy is continued For patients at high risk of HIT, it is proposed to monitor platelet count two to three times a week from days 4 to 14 of treatment, and then once a week for 1 mo if heparin therapy is continued. No retest No retest	ASH 2018 guidelines[42] 2020 French Working Group on Perioperative Haemostasis proposals[148] 2024 BSH guideline[193]
Thrombotic thrombocytopenic purpura	Test ADAMTS13 activity, prior to any treatment; but should not delay plasma exchange (PEX). BSH 2023 prefers testing for ADAMTS13 activity over using scoring systems (GRADE 2C), and Nine-I investigators recommend scoring systems if ADAMTS13 activity cannot be quickly measured. BSH 2023: Initial blood tests as part of TTP diagnosis include full blood count, reticulocyte count, blood film, lactate dehydrogenase, coagulation, B12/Folate, liver function, renal function, and troponin. Nine-I Investigators expert statement's laboratory workup for TTP: cardiac, neurological, renal, and gastrointestinal screening for organ dysfunction; blood cell counts and smear, lactate dehydrogenase, haptoglobin, bilirubin, direct antiglobulin test, basic coagulation tests, and tests for proteinuria and hematuria; bone marrow aspiration in patients with atypical TMA features or other diseases	Not otherwise specified (ISTH 2020). "ADAMTS13 activity 3 mo from diagnosis may [...] predict the risk of subsequent relapse" (BSH 2023). French Reference Center: assessed every trimester during clinical remission. Acute stage: diagnosis once then weekly after plasma exchange (PEX) until $\geq$50% Long-term follow-up: every 3 mo (Coppo et al)[189]	ISTH 2020 guidelines[187] BSH 2023 guideline[186] Nine-I Investigators expert statement[210] French Reference Center for Thrombotic Microangiopathies[211] Coppo et al[189]

(*Continued*)

Table 3 (*Continued*)

Indication	Diagnosis	Follow-up	References
Major bleeding and coagulopathy following trauma	*Patients treated or suspected of being treated with oral anticoagulants* In VKA-treated patients undergoing an emergency moderate-to-high bleeding-risk procedure, we recommend that INR must be measured on the patient's admission to the hospital (ESAIC, 1B) We suggest the measurement of plasma levels of oral direct antifactor Xa agents such as apixaban, edoxaban or rivaroxaban in patients treated or suspected of being treated with one of these agents (pan-European, Grade 2C) Pan-European guidelines suggest the measurement of DOAC plasma levels in patients treated or suspected of being treated with DOACs (pan-European, Grade 2C). *Other patients* We recommend the early and repeated monitoring of haemostasis, using either a traditional laboratory determination such as PT/INR, Clauss fibrinogen level and platelet count and/or POC PT/INR and/or a viscoelastic method (pan-European, Grade 1C)	According to the clinical presentation and evolution	2023 (sixth edition) pan-European guideline[126] 2022 (second update) ESAIC guidelines[150]

Abbreviations: ASH, American Society of Hematology; AT, antithrombin; BSH (/BCSH), British Society for Haematology (/British Committee for the Standards in Haematology); DIC, disseminated intravascular coagulation; ESAIC, European Society of Anaesthesiology and Intensive Care; HIT, heparin-induced thrombocytopenia; ISTH(/SCC), International Society on Thrombosis and Haemostasis (/Scientific and Standardization Committee); JSTH, Japanese Society on Thrombosis and Hemostasis; LMWH, low-molecular-weight heparin; mo, months; POC, point of care; PT, prothrombin time; SIC, sepsis-induced coagulopathy; SISET, Italian Society on Haemostasis and Thrombosis; TTP, thrombotic thrombocytopenic purpura; UFH, unfractionated heparin; VKA, vitamin K antagonists.

exacerbate bleeding by further increasing portal hypertension due to fluid overload.[117]

Another important aspect of understanding hemostasis in patients with cirrhosis is that the rebalanced hemostatic state seen in compensated cirrhotic patients can be perturbed by clinical events such as variceal bleeding, acute kidney injury, or inflammation. Such perturbations often result in a shift toward hypercoagulability.[118] At the same time, decompensation of cirrhosis may be associated with worsening disease severity or result in volume expansion, as seen in conditions such as acute kidney injury. This exacerbates portal hypertension and increases the risk of bleeding. The assessment of hemostasis in a patient with liver disease/cirrhosis must, therefore, consider its variability over time and the influence of specific clinical events. Hemostatic assessment cannot rely solely on standard coagulation tests such as PT ratio or aPTT and must take primary hemostasis, the whole coagulation system (including both pro- and anticoagulant factors), and fibrinolysis into account. Similarly, viscoelastometric assays (TEG/ROTEM) lack the sensitivity to detect VWF, as well as minor to moderate hyperfibrinolysis and natural anticoagulants. Finally, there is no standardization or interchangeability of results across different instrument technologies.[119]

Collectively, current tests for hemostasis are inadequate to assess the perioperative risk of bleeding. New tests such as thrombomodulin-modified thrombin generation validated by prospective design and clinical end points are urgently required.[120] Until results from these studies are available, clinicians should refrain from using traditional hemostasis tests and arbitrary cutoffs to make decision on perioperative prophylaxis.

Disseminated Intravascular Coagulation

It is notable that aPTT is not included in any of the scoring systems for overt DIC, the Japanese Association for Acute Medicine (JAAM) DIC, or sepsis-induced coagulopathy (SIC).[121] PT suffices. Consequently, it is inadvisable to utilize aPTT for diagnosing DIC. AT is included in the diagnostic criteria for DIC proposed by the Japanese Society on Thrombosis and Hemostasis (JSTH), but not by the International Society of Thrombosis and Hemostasis (ISTH). However, the ISTH has recently mentioned that AT activity and VWF are interesting biomarkers because changes in their plasma levels may reflect clinical severity and can be assessed easily in many clinical settings at the present.[121] Similarly, the measurement of fibrin monomers (FM)—FMs (half-life: 2–6 hours[122]), produced as a result of the action of thrombin on fibrinogen, are highly reactive molecules that assemble to form protofibrils but can also associate with two fibrinogen molecules, which limits their molecular mass so that they remain soluble, and thus accessible to measurement in plasma[122]—is included in the diagnostic criteria for DIC proposed by the JSTH but not by the ISTH. The SepsiCoag

multicentric prospective observational study on patients entering an ICU with septic shock has recently evaluated the prognostic potential of fibrin generation markers (FGMs) tested at inclusion in the study, on survival at day 30. FM was the FGM best related with late prognosis.[123] FMs were higher in nonsurvivors, whereas it was not the case for D-dimers or fibrin/fibrinogen degradation product (FDP) values. Similarly, a 2017 study[124] showed that FM is a more effective indicator than D-dimers for differentiating patients with overt DIC and non-overt DIC from non-DIC patients. However, it should be noted that FM is sensitive to several preanalytical artifacts: vigorous mixing, pneumatic tube system (PTS) use, the time interval between blood collection and centrifugation, tube underfilling, and tourniquet tightening (highly tight for more than 3 minutes).[125]

Major Bleeding and Coagulopathy Following Trauma

It is inadvisable to resort to aPTT and platelet function tests in the context of significant bleeding. In accordance with the sixth edition of the European Guideline on the Management of Major Bleeding and Coagulopathy following Trauma,[126] the routine use of point-of-care (POC) platelet function testing devices in trauma patients on antiplatelet therapy or with suspected platelet dysfunction is not recommended (Grade 1C). Moreover, only PT, Clauss fibrinogen level, platelet count, and/or POC PT/INR and/or a viscoelastometric method should be used for monitoring coagulation in the event of major bleeding (Grade 1C).[126]

Preoperative Screening

There is a strong misbelief that coagulation screen tests can provide a general overview of the overall hemostatic system so that having normal PT and aPTT reassures about normal hemostasis during an invasive procedure or surgery. However, coagulation screen does not reliably reproduce the physiological coagulation cascade, and those tests do not completely reflect many aspects of hemostasis including abnormalities in VWF, platelet function, factor XIII, natural coagulation inhibitors, and, last but not least, endothelial dysfunction. In addition, mild coagulation deficiencies are sometimes overlooked by PT and aPTT. Similarly, VETs do not show the whole coagulation process as they are not sensitive to von Willebrand factor and minor/moderate fibrinolytic activity as well as natural anticoagulants, and have limited sensitivity to platelet function.[119,127] In addition, POCTs are a cause of concern, because nonrestriction of ordering laboratory testing could lead to overuse. Therefore, normal or abnormal coagulation screen tests cannot make us certain that the patient will achieve adequate hemostasis during an invasive procedure or surgery.[70] Sensitivity and specificity of systematic PT, aPTT, and platelet count to identify patients with hemostasis abnormalities leading to an increased bleeding risk were only 44% (95% CI, 22–69%) and 93% (95% CI, 91–94%).[128]

Venous Thromboembolism-Thrombophilia

The large, multicenter international Computerized Registry of Patients with Venous Thromboembolism (RIETE) of >100,000 patients with VTE has recently studied the impact of heritable thrombophilia on anticoagulant management and clinical outcomes. Approximately 20% of all patients were tested for heritable thrombophilia. Clinical characteristics and VTE risk factors differed markedly between tested and untested patients with VTE. Testing for heritable thrombophilia was performed more frequently in younger patients, patients with VTE provoked by estrogen use, pregnancy or postpartum, unprovoked VTE, and prior VTE.[129] The ASH 2023 guideline[86] used a modeling approach to address 23 clinical questions. For patients with VTE, conditional recommendations for thrombophilia testing and subsequent continuation of anticoagulant treatment in those with thrombophilia were given only in the following scenarios: (1) for patients with VTE associated with nonsurgical major transient or hormonal risk factors and (2) for patients with cerebral or splanchnic venous thrombosis, in settings in which anticoagulation would otherwise be discontinued. For all other scenarios (i.e., unprovoked VTE as well as VTE provoked by major surgery), the panel provided conditional recommendations against testing for thrombophilia. However, these recommendations suffer from certain limitations that may have potentially generated inappropriate recommendations, as recently illustrated by Djulbegovic et al.[130] The BSH guideline on thrombophilia testing used more pragmatic approach, endorsing the recommendations based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature to evaluate levels of evidence and to assess the strength of recommendations.[131] Recommendations on thrombophilia testing in various clinical scenarios by the BSH and ASH guidelines are summarized in ►Table 4. The ASH-ASPHO Choosing Wisely Campaign recommends avoiding thrombophilia testing in children with venous access-associated thrombosis and no positive family history.[132] In conclusion, clinical practice data from the RIETE Registry in patients with VTE confirms that testing for inherited thrombophilia is widely performed despite lack of evidence on their clinical predictive values and no influence in clinical management. Recommendations derived from the guidelines are still based on indirect evidence, and whether and how thrombophilia testing should inform clinical decisions requires additional clinical evidence.

Interferences

Certain clinical circumstances have the potential to impede the accuracy of hemostasis tests. For example, according to BSH guidelines, thrombophilia testing should be avoided in patients who have experienced a recent VTE event to allow complete restoration of physiological inhibitors after the acute episode of thrombosis and avoid unreliable, namely, false positive, test results.[133] However, according to the French guidelines, thrombophilia testing may be performed in acute thrombosis but results of LAC, AT, PC, and PS testing during an acute phase response should be interpreted with caution, as false-positive and -negative results can occur.[28] Performing AT and PC at the acute phase allows the exclusion of a defect in case of normal results.[134,135] Similarly, VKAs

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Table 4 Comparison of two guidelines (BSH and ASH) on recommendations for thrombophilia testing in specific acute settings

Clinical scenario	BSH 2024 guideline[193]	Level of evidence (grade)	ASH 2023 guideline[86]	Level of evidence	Comment
General	Testing for inherited thrombophilia after a venous thrombotic event is not routinely recommended to guide clinical management	2B	Patients with symptomatic VTE, unspecified type of VTE (i.e., not specified as provoked or unprovoked VTE): Do not test for thrombophilia	Conditional, very low level of evidence	Agreement
Timing of thrombophilia testing following acute thrombosis	Testing for deficiencies of physiological anticoagulants should be performed only after 3 mo of anticoagulation for acute thrombosis	2B	Not addressed	/	Nota. Disagreement between BSH and French guidelines
Testing for aPL following unprovoked VTE	Testing is recommended as results may guide clinical management including the choice of antithrombotic therapy	1B	Testing is not recommended	Conditional, very low level of evidence	Discordance
Testing for aPL following VTE provoked by a minor risk factor	Testing is suggested as results may guide clinical management including the choice of antithrombotic therapy	2C	Testing is not recommended following VTE-associated major risk surgical or non-surgical major risk factor, pregnancy/postpartum, or oral contraceptives	Conditional, very low level of evidence	The definition of a minor risk factor is not specified in BSH guidelines
Assessment of possible CAPS in patients with acute multiple thrombosis	Patients with acute multiple thrombotic events and evidence of organ failure suggestive of CAPS should be tested for antiphospholipid antibodies	1A	Not addressed	/	/
Thrombosis at unusual sites (testing for heritable thrombophilia)	Testing is not recommended as the association is weak and clinical management would not be changed if thrombophilia defects are found	2B	Testing is recommended only if anticoagulation would otherwise be discontinued after primary short-term period treatment	Conditional, very low level of evidence	Agreement
Thrombosis at unusual sites (testing for aPL)	Testing is recommended in the absence of clear provoking factors as the type and duration of anticoagulation are influenced by the presence of these antibodies	1A	Testing (including aPL) is recommended only if anticoagulation would otherwise be discontinued after primary short-term period treatment	Conditional, very low level of evidence	Discordance
Thrombosis at unusual sites (testing for PNH)	Testing for PNH is suggested with abnormal hematological parameters (i.e., cytopenia and abnormal red cell indices) or evidence of hemolysis (i.e., increased lactate dehydrogenase, bilirubin, and reticulocyte count)	2C	Does not mention about PNH testing	/	Discordance

Table 4 (*Continued*)

Clinical scenario	BSH 2024 guideline[193]	Level of evidence (grade)	ASH 2023 guideline[86]	Level of evidence	Comment
Thrombosis at unusual sites (testing for MPN panel)	Testing for MPN panel (including *JAK2* V617F, *JAK2* exon 12, *CALR*, *MPL* mutation analysis) is recommended in the presence of full blood count abnormalities suggestive of an MPN	1C	Does not mention about MPN testing	/	Discordance
Thrombosis at unusual sites (testing for *JAK2* mutation)	Testing for *JAK2* mutation is suggested in splanchnic vein thrombosis or cerebral venous sinus thrombosis in the absence of clear provoking factors and a normal full blood count	2C	Does not mention about *JAK2* mutation testing	/	Discordance
Testing for aPL in patients with RVO	Testing may be considered in the absence of any other risk factors associated with RVO	2C	Does not discuss about RVO and thrombophilia testing	/	Discordance
Arterial thrombosis	Testing for inherited thrombophilia is not recommended	1B	Not addressed	/	/
aPL testing in arterial thrombosis	Testing is recommended in the absence of other vascular risk factors	1B	Not addressed	/	/
PNH and MPN testing in arterial thrombosis	Testing is considered if abnormal blood parameters suggestive of MPN or PNH	2C	Not addressed	/	/
Ischemic stroke, all types except cerebral venous sinus thrombosis Testing for heritable thrombophilia	Testing is not recommended	1A	Not addressed	/	/
Ischemic stroke, all types except cerebral venous sinus thrombosis Testing for aPL	Testing should be considered in young (<50 years of age) in the absence of identifiable risk factors for cardiovascular disease	1A	Not addressed	/	/
Ischemic stroke, all types except cerebral venous sinus thrombosis Testing for PNH/MPN	Consider testing with an abnormal full blood count	2C	Not addressed	/	/
Thrombophilia testing in stroke and patent foramen ovale closure	Testing is not suggested	2C	Not addressed	/	/
Thrombophilia testing in children with purpura fulminans	Urgent testing for protein C and S deficiency is recommended	1B	Not addressed	/	/
Thrombophilia testing neonatal stroke	Routine testing is not recommended	2B	Not addressed	/	/

(*Continued*)

Table 4 (*Continued*)

Clinical scenario	BSH 2024 guideline[193]	Level of evidence (grade)	ASH 2023 guideline[86]	Level of evidence	Comment
Thrombophilia testing in neonatal thrombosis	With multiple unexplained thrombosis, especially with clinical evidence suggestive of CAPS, testing for aPL and heritable thrombophilia should be considered	2D	Not addressed	/	/
Heritable thrombophilia testing in pregnancy complications	Recommended against thrombophilia testing	2B	VTE provoked by pregnancy or postpartum: test for thrombophilia	Conditional, very low level of evidence	Discordance
aPL testing in pregnancy complications	Screening for aPL can be considered with recurrent or late pregnancy loss, as the results aid risk stratification and treatment decisions	2B	Does not mention about aPL testing in pregnancy complications	Conditional, very low level of evidence	Discordance

Abbreviations: aPL, antiphospholipid antibodies; CAPS, catastrophic antiphospholipid syndrome; mo, month; MPN, myeloproliferative neoplasms; PNH, paroxysmal nocturnal hemoglobinuria; RVO, retinal vein occlusion; VTE, venous thromboembolism.

such as warfarin must be suspended and switched to a suitable alternative anticoagulant such as LMWH (sample for testing should be taken just prior to the next dose of LMWH) before testing for thrombophilia (especially for LAC, activated protein C resistance, PC, and PS).[136] aPTT-based assay should not be performed, whereas dRVVT may be performed but interpreted with caution if INR[137] is between 1 and 3. Furthermore, acute inflammation, which is a common occurrence in acute patients, can interfere with LAC assays based on aPTT and dRVVT.[138] Consequently, these assays should be used in such patients with much caution. Finally, when thrombophilia testing is performed at least 3 to 6 months after an acute episode of VTE results in patients requiring longer anticoagulation, DOAC removal agents may be used to avoid interference of DOACs.[139–142] However, despite the use of DOAC removal agents, very low DOAC levels (below the detection threshold) may impact dRVVT.

Conclusion

Inappropriate use of laboratory resources is common and may have serious adverse consequences. Implementation of guidance-based interventions is an effective strategy to reduce inappropriate use of hemostasis testing. However, few interventions use evidence-based guidance/recommendations for testing when providing indications for testing, even when these guidance/recommendations are available. A deeper understanding of the factors contributing to the underutilization of existing guidelines (i.e., based on low evidence) would prove invaluable in the future when designing interventions to reduce inappropriate laboratory testing. In this review, we aimed to provide a summary of guidance available for the most commonly prescribed hemostasis tests in the acute setting. We emphasize the importance of involving laboratory specialists in the design of guidelines and working in close collaboration with clinicians. Diagnostic workup could be greatly enhanced if the laboratory would receive clinical information (e.g., which clinical question needs to be answered? what is the pretest probability of the condition searched for?) and test results would be given with a comment on their clinical relevance (e.g., risk profile of antiphospholipid antibodies, likelihood ratio [or even better negative predictive value/positive predictive value] of the quantitative test result).

Authors' Contribution

L.D. and F.M. contributed to the design of the manuscript. L.D. and F.M. drafted the manuscript and tables. D.J.A., M.H., A.M., E.C., M.C., I.G-T., C.F., T.L., L.A., J.C., G.L., and F.M. substantially revised and enhanced the manuscript. All authors approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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