Quality in Laboratory Hemostasis and Thrombosis

Second Edition

Edited by
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and F. Eric Preston

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Contents

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Foreword

Thou art always figuring diseases in me, but thou art full of error: I am sound

(William Shakespeare. Measure for measure (1604); Act I, Scene II)

A correct diagnosis is the cornerstone of medicine. Without it, no remedy can be prescribed, or prognosis given. Although laboratory tests are only a part of the diagnostic arsenal, together with history taking, clinical examination, and imaging techniques, few diagnoses are arrived at without some form of laboratory test. Inadequate tests may lead to either false reassurance or false alarm. They may lead to the erroneous choice not to give treatment when treatment would be beneficial, or even to prescribe the wrong treatment, which is likely to be harmful. It is therefore of the utmost importance that whenever laboratory tests are performed, the results are reliable.

Laboratory tests in the field of thrombosis and hemostasis are notoriously difficult, which is related to the large variety in techniques that are used, and the sensitivity of many assays to small preanalytical and analytical variation. Therefore, quality assurance is crucial, and no hemostasis laboratory can afford not to invest in internal and external quality control. The book, Quality in Laboratory Hemostasis and Thrombosis, edited and written by authorities in the field, since its first edition in 2008, has become a indispensable help for those who wish to set up a hemostasis laboratory, as well as those who already work in such a place. For, to quote from the first chapter: “Process is never optimized; it can always be improved.”

The book has two parts: the first eight chapters give a scholarly overview of the concepts that underlie quality

assurance, explaining the various aspects of test validation, with its components, of which accuracy and precision are the most important: does a test measure what it is supposed to measure, and does it do so with acceptable reproducibility. Subsequent chapters in this first part explain in detail how internal quality control deals with precision and external quality control with accuracy. The development of international standards is an important and ongoing development in improving accuracy and comparability of hemostasis laboratory tests. Here, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, working together with the World Health Organization, has played a major role. Over the years we have witnessed the emergence of large external quality assurance programs, in which samples are sometimes sent to more than a thousand participating laboratories. Such programs not only allow laboratories to evaluate their performance, but also to group results by reagent or instrument, which leads to valuable insights, and further quality improvement. Newly added chapters to the second edition deal with the causes of laboratory error, the understanding of which is indispensable in optimizing laboratory performance, and the performance and interpretation of hemostatic tests in children.

In the second part of the book, Chapters 9 through 23, a detailed description is given of all major assays in hemostasis, grouped in a series of chapters on coagulation factor assays, on primary hemostasis (platelets and von Willebrand factor), and on thrombophilia testing and anticoagulant treatment monitoring. These chapters give the reader invaluable information on the performance and interpretation of these tests. A newly added chapter that was much missed in the first edition deals with heparin-induced thrombocytopenia.

The ultimate test for a laboratory test is whether it improves medical care, that is, reduces morbidity and mortality, which depends on the effect a negative or positive test result has on the treatment of a patient. A test that does not affect clinical management is a waste of resources. Both at the beginning and the end of laboratory tests there is usually a clinician, who first makes the decision to order a test, and subsequently has to interpret the test result. Although these clinical decisions and interpretation are not part of the content of this book, which would have made it unwieldy to say the least, these are of obvious importance, and one of the tasks of the individuals working in hemostasis laboratories is to educate clinicians about the clinical value of the various assays. I am quite confident that in the field of hemostasis and thrombosis more useless than useful testing is done, and that in medicine as a whole the greatest waste of money is on redundant diagnostics. The practice of medicine knows a wide variety of tests, which generally serve three purposes, either to diagnose a disease, or to test for a risk factor for disease, or to screen for either of these. This distinction is rarely sharply made, while it seems that clinically one type (diagnosing a disease) is almost always indicated and useful, and another type (testing for risk factors) only rarely is. While it is logical to find out which disease a patient with complaints has, it is not so logical to try and identify the causes of that disease, or even to try and identify those risk factors in nondiseased individuals, such as relatives of individuals with thrombosis. The reason the distinction between diagnosing a disease and identifying a risk factor is not always sharply made, is possibly because in some diseases in the field, notably bleeding disorders, there is an almost one-to-one relationship between the cause of the disease and the disease itself. While excessive bleeding is the disease and the clotting factor level a cause, individuals with no factor VIII or IX will invariably have the clinical

disease of hemophilia, and therefore, measuring the clotting factor level has become synonymous to diagnosing hemophilia. This is quite different for thrombosis. Thrombosis (deep vein thrombosis or pulmonary embolism) is a disease, whereas thrombophilia is not. Given the multicausal nature of the etiology of thrombosis, in which multiple risk factors need to be present to lead to disease, it is far from self-evident that testing for thrombophilic abnormalities has any clinical value. So far, there are no clinical studies that show a benefit of such testing, although it is performed on a broad scale. Whenever you order a test or are requested to perform a test, question whether the result could possibly change anything. If not, or if the only benefit is to satisfy the doctor's curiosity, the test should not be done.

The reliability of a particular assay should be viewed in the context in which the test is ordered. Suppose one would order a test for high factor VIII as a prothrombotic risk factor, the above mentioned notwithstanding, an error of five IU/dL would be irrelevant, since the purpose is to discriminate between levels of over 150 or 200 IU/dL versus plasma concentrations around 100 IU/dL. The same error in a factor VIII assay to diagnose hemophilia A could be disastrous.

A clinician, when ordering a test, will have to deal with so-called prior probabilities, which is of particular relevance in screening tests. A slightly prolonged aPTT has a vastly different meaning when found in a healthy woman who had four uneventful deliveries who has come to the hospital for a tubal ligation, than in an 18-month-old boy who needs to undergo a duodenoscopy with possible biopsies. She is unlikely to have a bleeding tendency, even when the aPTT is prolonged, while the young boy may suffer from hemophilia. Screening tests affect the likelihood of disease, which, according to Bayes' theorem, is also a function of the prior

probability of disease. Virtually, all tests that use reference ranges based on statistical cutoff values, such as the population mean plus or minus two standard deviations, are screening tests, that do neither establish a risk factor or a disease, but only, when abnormal, affect the likelihood of that state. Nature does not use standard deviations, and using a cutoff of two standard deviations by definition finds 2.5% of the population below, or over, such a cutoff. In reality, diseases and risk factors may have prevalences that exceed, or, more usual, lie far below this figure. Tests using “normal ranges” therefore can never establish an abnormality, and should be followed by more specific tests, such as clotting factor assays or genetic tests.

Over the last decades, major progress has been made in quality assurance of hemostatic laboratory assays. In this new edition of Quality in Laboratory Hemostasis and Thrombosis, all chapters have been updated and several new chapters have been added. This book will remain an indispensable part of every hemostasis laboratory, where, given its hand-on nature, it will rarely sit to get dusty on the shelves.

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