

## Preface

## Laboratory Diagnostics for Thrombosis and Hemostasis Testing—Part II

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Welcome to a second themed issue of *Seminars in Thrombosis and Hemostasis* dedicated to laboratory diagnostics. In this issue, we will present several state-of-the-art reviews highlighting hemostasis/thrombosis testing aspects relevant to a spectrum of bleeding and thrombotic disorders and treatments. The issue begins with a contribution by Adcock et al summarizing the performance of mixing studies to further evaluate the etiology of prolonged clotting times and differentiate factor deficiencies from factor inhibitors, inhibitor anticoagulants, and lupus anticoagulants.<sup>1</sup> Due to technical and interpretive non-standardization, combined with patient variables, there is no single approach to mixing studies that will correctly classify all cases as a deficiency or an inhibitor. Because mixing study results are often used as an early test to help determine what additional specialized testing is needed, it is vitally important to understand the pre-analytical, analytical, and post-analytical variables that affect the testing, including when the result patterns may be misleading. This review is an excellent summary of the variables that must be considered with each situation.

The second manuscript, by Saadalla and colleagues, provides an informative review of traditional and partially automated von Willebrand factor multimeric analysis, and the role of multimers in discriminating different subtypes of von Willebrand disease (VWD).<sup>2</sup> The review includes discussion of VWD subtypes, underlying pathophysiology, and abnormalities of triplet or quintuplet structure that can be seen on multimer gels. The third contribution, authored by Keiji Nogami, describes clot waveform analysis (CWA), an information analysis method that is available on certain coagulation laboratory instruments.<sup>3</sup> The method deconstructs the coagulation pathway of the prothrombin time or activated partial thromboplastin time into phases such as the pre-coagulation phase, coagulation phase, and post-coagulation phase. Potential applications of CWA mentioned in the review include predicting the phenotype of inherited or acquired coagulation factor abnormalities. CWA is a global coagulation assay that may provide useful information in

several challenging hemostasis settings, although standardization of testing and additional study is necessary to move the application forward in clinical practice. The fourth manuscript, by Larsen and colleagues, focuses on the current status of platelet function testing in the diagnosis of bleeding disorders and to monitor the efficacy of antiplatelet therapy, including descriptions of available methods and advantages and disadvantages of each.<sup>4</sup> Pre-analytical variables affecting platelet function are discussed in detail and can help the reader address common practical challenges in their own laboratories.

The subsequent manuscript, by Bowyer and Gosselin, focuses on factor VIII and IX activity measurements for hemophilia diagnosis and treatment.<sup>5</sup> The article opens with a summary of the impressive advances in hemophilia care over the last decade and then transitions to discussion of types of coagulation factor assays and the variables that can impact results. Importantly, the discordance between the one-stage and the two-stage chromogenic assays seen in a subset of nonsevere hemophilia patients is described, as it relates to testing approaches for diagnosis of mild hemophilia. The manuscript then summarizes the currently available modified, extended half-life factor replacement products and the recommended (and not recommended) laboratory methods for monitoring these products, information of great value to clinical hemostasis laboratories.

In the next manuscript, authors Warkentin and Greinacher provide an excellent review on laboratory testing for heparin-induced thrombocytopenia (HIT), including the autoimmune and spontaneous forms, as well as vaccine-induced immune thrombotic thrombocytopenia (VITT).<sup>6</sup> While these highly prothrombotic conditions share the characteristics of thrombocytopenia and increased thrombotic risk, the antibodies in HIT and VITT are distinct in their recognition of distinct PF4 epitopes, which impacts the sensitivity and specificity of laboratory assays. In particular, while ELISA methods are typically able to identify both types of antibodies, rapid immunoassays have high sensitivity for HIT but poor sensitivity for VITT. This is an incredibly

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importance difference in laboratory practice, with potential to significantly impact patient diagnosis and care, and readers are urged to read this manuscript carefully. An excellent figure demonstrating the HIT and VITT antibody differences was selected as the cover art for this issue.

The next article in this issue, from Gardiner et al, delves into the discussion of laboratory developed tests (LDTs), assays that are more commonly performed in highly specialized hemostasis/thrombosis laboratories, and that fill an important niche for patient testing when there are no commercially available options approved by local regulatory authorities, or the commercial options are of substandard quality.<sup>7</sup> The manuscript provides important background context on differences in laboratory regulation in different parts of the world, and explores the challenges associated with increasing LDT regulation with potential impacts to patient care. The manuscript provides helpful tables that summarize studies that should be performed during the validation of a high-quality LDT.

In the next review, Richard Marlar expertly discusses diagnosis of inherited defects in the natural anticoagulants antithrombin, protein C, and protein S.<sup>8</sup> Deficiencies in these proteins are prominent inherited causes of increased thrombotic risk. However, diagnostic testing is not always necessary for patient management and the tests are greatly affected by pre-analytical variables, technical challenges including assay interference by anticoagulant medications, and problems with interpreting results and applying these results to patient care. The author thoughtfully discusses testing approaches and algorithms recommended by the International Society on Thrombosis and Hemostasis (ISTH) for evaluating these deficiencies<sup>9–11</sup> and arms the reader with practical knowledge to avoid common pitfalls.

In the last manuscript, authors Pruthi and Chen discuss the bypassing agents used to treat hemophilia A and B patients with factor inhibitors, including treatments currently used and those in development.<sup>12</sup> The review focuses on what is known about the effects of these agents on routine and specialized coagulation assays.

We are thrilled to present this issue of *Seminars in Thrombosis and Hemostasis* composed of an excellent collection of laboratory state-of-the-art reviews. We thank the

expert authors for their contributions and hope the readers find great value in the content.

#### Conflict of Interest

None declared.

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