Heparin-induced thrombocytopenia in 2017 and beyond

Tamam Bakchoul1; Andreas Greinacher2; Theodore E. Warkentin3

1Center for Clinical Transfusion Medicine, University of Tübingen, Germany; 2Institute for Immunology and Transfusion Medicine, Universitätmedizin Greifswald, Germany; 3Department of Pathology and Molecular Medicine, and Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

As Guest Editors, it gives us great pleasure to write this editorial regarding the eight papers comprising the Theme Issue, “Heparin-induced thrombocytopenia”, published in Thrombosis and Haemostasis. Heparin-induced thrombocytopenia (HIT) is an important “clinical-pathological” syndrome (1, 2) that continues to cause considerable patient harm world-wide. This prothrombotic disorder is caused by immunisation against platelet factor 4 (PF4) after complex formation with heparin or other polyanions. A subset of anti-PF4/heparin antibodies is capable of intravascular activation of platelets and monocytes by cross-linking Fcy receptors IIA (FcyRIIA), leading to platelet count decrease (thrombocytopenia) and/or thrombosis. HIT is often associated with devastating complications such as life- and limb-threatening thrombosis, making it one of the most serious adverse drug reactions in medicine.

This Theme Issue highlights the pathophysiology of HIT, emphasising its clinical features and the role of laboratory assays detecting the pathogenic antibodies. In the first part, comprising four papers (3-6), various “basic” aspects of HIT are discussed, including the structure of HIT antigens, the immune pathogenesis, and the role of Fcy receptors in mediating the disorder through platelet activation, as well as the non-platelet effector cells, monocytes and endothelial cells.

In the first article, Delcea and Greinacher present an update on current biophysical tools that have been successfully used to identify features that make the “self” molecule, PF4, immunogenic (3). Complex formation between (cationic) PF4 and (polyanionic) heparin has a cardinal role in the pathophysiology of HIT. PF4 undergoes conformational changes after binding to heparin, inducing neoepitopes that are recognised by pathogenic HIT antibodies. In this chapter the authors present state-of-the-art approaches to study the biophysical characterisation of PF4 when complexed with different polyanions, and the biophysical interactions of PF4/polyanion complexes with HIT antibodies, including some data on their effects on platelets. The findings provided by biophysics may be used to develop new polyanionic drugs with a reduced risk for HIT (e.g. nucleic acid-based drugs) and to guide future diagnostic and treatment strategies. These novel methods and techniques could also be promising tools to understand the mechanisms underlying the atypical features of the HIT immune response, as well as other antibody-mediated disorders in thrombosis and haemostasis, such as acquired hemophilia and thrombotic thrombocytopenic purpura.

By identifying the structural requirements for PF4 immunogenicity, biophysical studies alongside animal models have provided insights into the distinct features of the HIT immune response. The origin of the atypical temporal feature of the humoral immune response against PF4/heparin complexes is discussed in the article by Khandelwal and Arepally (4). The authors present data suggesting that previous bacterial infection(s) may play a central role in priming the immune response against PF4/polyanions as an explanation for the rapid evolution of an isotype-switched HIT immune response following heparin exposure. Although murine studies were helpful to better characterise the cellular basis of the immune response in HIT, a number of fundamental issues remain unclear, such as whether T-cells are essential, and what regulatory mechanisms keep the immune response in check. More efforts are needed to identify risk factors for the breakthrough of the autoimmune response in HIT.

In contrast, the role of platelet activation in the pathogenesis of HIT is less controversial. IgG immunisation against PF4/heparin complexes is a frequent finding even in heparin-naive individuals. However, only a minority of sensitised patients develop clinically-evident HIT upon heparin exposure. This is because only a subset of the antibodies generated is able to activate platelets via cross-linking of the FcyRIIA. Rollin et al. discuss the critical role of these receptors in the pathophysiology of HIT (5). In particular, the potential influence of several FcyRIIA gene variations (i.e. H131R polymorphism), as well as in its signalling proteins (i.e. CD148, a protein tyrosine phosphatase that positively regulates Src kinases in platelets), on the development of HIT and HIT-associated thrombosis, are addressed. Identifying a strong role for genetic risk factors for the clinical outcomes in HIT seems, however, to be unlikely, since HIT is a multifactorial disorder and various non-genetic risk factors may play important roles, depending on patients’ underlying diseases and various comorbidities.

In the next paper, Madeeva et al. discuss the various platelet-independent pathways that are involved in the pathophysiology of HIT (6). These authors present the intriguing concept that HIT antibodies induce increased procoagulant activity by priming monocytes and endothelial cells to bind PF4 with higher avidity than platelets. Most interesting is their idea that pathogenic antibodies bound to endothelial cells could promote prothrombotic conditions by a mechanism that is independent of FcyR activation. Targeting these processes by novel specific signalling inhibitors, such
as Syk inhibitors, might be an attractive therapeutic strategy to prevent complications, with less adverse impact on systemic haemostasis than current approaches.

The second part of this Theme Issue, also comprising four articles (7–10), discusses clinical and management issues, such as the clinical picture of HIT (and how it differs from mimicking syndromes of non-HIT thrombocytopenia) and the use of different laboratory tests to detect the presence of antibodies, both pathogenic and non-pathogenic. This section also includes two papers dealing with patient management, one that emphasises general treatment principles and the other addressing special considerations in the critically ill population.

Warkentin describes the clinical features of HIT from the perspective of the 4Ts scoring system, discussing the sometimes subtle features that can be helpful in distinguishing between HIT and non-HIT thrombocytopenia (7). Of particular interest is the focus on an important subset of HIT antibodies with “autoimmune” features, where highly pathogenic IgG activate platelets even in the absence of pharmacological heparin. This phenomenon explains such unusual presentations including: delayed-onset, persisting, spontaneous, and fondaparinux-associated HIT. This paper also summarises four different syndromes of fondaparinux-associated HIT; ironically, despite the (rare) possibility of fondaparinux triggering or exacerbating HIT, the author advocates using fondaparinux for treatment of HIT. Finally, several HIT-mimicking syndromes are described, including abciximab-induced thrombocytopenia of delayed-onset, venous limb gangrene complicating cancer-associated disseminated intravascular coagulation (DIC), and the recently described acute DIC/hepatic necrosis-limb necrosis syndrome.

The diagnosis of HIT based solely on clinical information is challenging due to the ubiquity of heparin use and the high frequency of non-HIT thrombocytopenia among hospitalised patients exposed to heparin. Nagler and Bakhchoul discuss the characteristics and diagnostic accuracy of current laboratory tests and clinical scoring systems (8). A special focus of this paper is on diagnostic approaches that might be used to improve the specificity of laboratory assays. Fine-tuning well-defined diagnostic algorithms to the individual setting is one of the challenges addressed.

In the next article, Cuker addresses the management of HIT based on a novel classification of five sequential phases of diagnosis and treatment: suspected HIT, acute HIT, subacute HIT A, subacute HIT B, and remote HIT (9). Each phase is associated with a unique set of clinical challenges and questions. Diagnostic and therapeutic approaches are discussed and specific recommendations provided.

Finally, the paper by Selleng and Selleng focuses on HIT issues pertaining to patients undergoing cardiac surgery and in the critically ill (10). Most importantly, short-term re-exposure to heparin, especially given intraoperatively to permit cardiovascular surgery, is discussed as a reasonable therapeutic option in patients with a history of HIT. This chapter also includes information on management of special situations, such as on- and off-pump cardiac surgery, and patients with ventricular assist devices.

Despite the progress in understanding the pathophysiology of HIT, the underlying immune mechanisms are still not well understood. HIT is one of the very few immune disorders allowing clinical studies of the early phase of an immune response in humans, as many patients receive heparin and the time window of the immune response is well-defined. Understanding the immune mechanisms underlying HIT may help to better understand other autoimmune disorders. From a clinical perspective, despite the increasing use of (less immunogenic) low-molecular-weight heparins and (non-HIT-inducing) non-heparin anticoagulants, HIT still occurs, often affecting critically ill patients who would otherwise still require unfractionated heparin. There still remain numerous diagnostic and treatment challenges, especially in critically ill patients, including the difficulty in distinguishing between HIT and non-HIT thrombocytopenia, and the dilemma of choosing the right anticoagulant when heparin is contraindicated due to HIT in thrombocytopenic patients with impaired renal or hepatic function.

Conflicts of interest
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References