JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 67, NO. 21, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2016.02.073

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Heparin-Induced Thrombocytopenia

A Comprehensive Clinical Review

Benjamin S. Salter, DO,[a] Menachem M. Weiner, MD,[a] Muoi A. Trinh, MD,[a] Joshua Heller, MD,[a] Adam S. Evans, MD,[a] David H. Adams, MD,[b] Gregory W. Fischer, MD[a]

ABSTRACT

Heparin-induced thrombocytopenia is a profoundly dangerous, potentially lethal, immunologically mediated adverse drug reaction to unfractionated heparin or, less commonly, to low-molecular weight heparin. In this comprehensive review, the authors highlight heparin-induced thrombocytopenia's risk factors, clinical presentation, pathophysiology, diagnostic principles, and treatment. The authors place special emphasis on the management of patients requiring procedures using cardiopulmonary bypass or interventions in the catheterization laboratory. Clinical vigilance of this disease process is important to ensure its recognition, diagnosis, and treatment. Misdiagnosis of the syndrome, as well as misunderstanding of the disease process, continues to contribute to its morbidity and mortality.
(J Am Coll Cardiol 2016;67:2519–32) © 2016 by the American College of Cardiology Foundation.

Unfractionated heparin (UFH) and other heparin derivatives, such as low-molecular weight heparin (LMWH), are among the most frequently prescribed medications worldwide (1). They are routinely used for therapeutic and prophylactic anticoagulation in a multitude of medical and surgical conditions (2). Although hemorrhagic events are the most common complication of heparin therapy, thrombotic complications are also possible in patients who develop heparin-induced thrombocytopenia (HIT) (3). Mortality associated with HIT is reported at between 20% and 30% (4,5).

HIT is a dangerous, potentially lethal, immunologically mediated adverse drug reaction to UFH or, less commonly, to LMWH (6,7). An older nomenclature defined 2 types of HIT: type I and type II (8). Type I, seen in 10% to 30% of patients given heparin, was characterized by a benign, mild thrombocytopenia occurring in the first 2 days after heparin administration (9). Platelet count spontaneously normalizes, even with continued heparin therapy, and is not associated with increased thrombotic risk (10–12). Type II refers to the antibody-mediated, potentially fatal disorder, now referred to as HIT, in which heparin therapy needs to be discontinued as soon as the diagnosis is suspected (10,13,14). It also requires the implementation of an alternative anticoagulation strategy to prevent the development of HIT with thrombosis (HITT) (15).

In this comprehensive review, we highlight HIT's risk factors, clinical presentation, pathophysiology, diagnostic principles, and treatment. We place special emphasis on the management of patients requiring procedures using cardiopulmonary bypass (CPB) or interventions in the catheterization laboratory. Increased awareness of this condition among clinicians is important to ensure its early recognition and treatment, to avoid serious complications (1). Misdiagnosis of the syndrome, as well as misunderstanding of the disease process, continues to contribute to its morbidity and mortality (11).

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Anesthesiology, Mount Sinai Medical Center, New York, New York; and the [b]Department of Cardiac Surgery, Mount Sinai Medical Center, New York, New York. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. John A. Bittl, MD, served as Guest Editor for this paper.

Manuscript received December 22, 2015; revised manuscript received February 3, 2016, accepted February 8, 2016.

ABBREVIATIONS AND ACRONYMS

ACCP = American College of Chest Physicians

ACT = activated clotting time

aPTT = activated partial thromboplastin time

CPB = cardiopulmonary bypass

DTI = direct thrombin inhibitor

ECT = ecarin clotting time

ELISA = enzyme-linked immunosorbent assay

FDA = U.S. Food and Drug Administration

HIT = heparin-induced thrombocytopenia

HITT = heparin-induced thrombocytopenia with thrombosis

IgG = immunoglobulin G

INR = international normalized ratio

LMWH = low-molecular weight heparin

PCI = percutaneous coronary intervention

PF4 = platelet factor 4

UFH = unfractionated heparin

INCIDENCE, EPIDEMIOLOGY, AND RISK FACTORS

Studies indicate that the prevalence of HIT ranges from 0.1% to 5.0% in patients receiving heparin (3,8,16,17), with about 25% to 50% of these patients developing HITT (9,18). The risk for developing HIT varies considerably according to several patient- and drug-related factors (3,8,16). The parameters most strongly associated with an increased risk for the development of HIT are: 1) the duration of heparin therapy; 2) the type and dose of heparin administered; 3) the indication for treatment; and 4) the patient's sex.

Prolonged exposure to heparin therapy (>5 days) has been shown to be a frequent risk factor for developing thrombocytopenia and the further development of HIT (19–21). UFH conveys a risk 10 times greater than that of LMWH (22–26), whereas the pentasaccharide fondaparinux is rarely associated with HIT, having been described in only a few case reports (27,28). Also, the origin of heparin affects the risk, with bovine UFH associated with a higher risk than porcine UFH (19,29). Therapeutic anticoagulation doses frequently result in greater platelet reductions; in HIT, however, even exposure to very small amounts of heparin (heparin flushes) can lead to the formation of HIT antibodies (21,30).

With regard to the indication for heparinization, surgical (particularly cardiac and orthopedic) or trauma patients (1% to 5%) have a far greater risk than medical or intensive care unit patients (<1%) for the development of HIT (31,32).

And finally, female patients have approximately twice the risk for developing HIT, often attributed to their increased immune responses (19,20,22,23,26,33,34).

CLINICAL PRESENTATION

The main clinical presentation of HIT is thrombocytopenia. After heparin exposure, platelet numbers decline rapidly, sometimes by 50% or more from baseline. Platelet counts fall below 150×10^9/l in 90% of patients, with a median nadir of about 55×10^9/l (35). There are 3 patterns of onset for HIT: rapid, typical, and delayed. Sixty percent of patients with HIT exhibit the typical pattern, resulting in a platelet decline 5 to 10 days after exposure. In 30% of cases, the onset pattern is rapid, where platelet numbers decline immediately post-exposure (4,35). Such a robust response can be the result of previous exposure to heparin in the past 100 days and residual antibody presence from heparin sensitization (35). Last, the remaining patients exhibit delayed-onset HIT, occurring an average of 9.2 days after initiating therapy; however, signs and symptoms can appear up to 3 weeks post-exposure (35).

Frequently, post-surgical patients exhibit a unique bimodal pattern of platelet decline. Initially, they may develop thrombocytopenia on post-operative day 1, but this usually rebounds in 5 to 6 days (36–38). A second decline in platelet count is more likely to be associated with HIT and should warrant further investigation (23,37–40). Importantly, clinicians should use the new, post-operative platelet count as a baseline.

Although HIT is characterized by thrombocytopenia, the disease process results in a paradoxical, prothrombotic disorder, with an incidence of thrombosis ranging from 50% to 89% in untreated patients (1,4,6,23,41). It can lead to devastating arterial and venous thromboembolic complications, including pulmonary embolism, mesenteric ischemia, ischemic limb necrosis, acute myocardial infarction, and stroke (5,6,8,42). Venous thromboses predominate over arterial thromboses in medical patients with HIT or following orthopedic surgery (40), whereas arterial and venous thromboses occur with similar frequency following vascular and cardiac surgery in patients with HIT (7). Additionally, 10% to 20% of patients have localized skin necrosis at heparin injection sites (4,5), and up to 20% of patients can develop disseminated intravascular coagulation (43).

However, when the clinical picture includes thrombocytopenia, it is important to review the multiple scenarios that should be included in the differential diagnosis. These disease processes include acute pulmonary embolism, end-stage renal disease, sepsis, and patients with recent CPB, indwelling arterial devices (e.g. intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation), and medications (4,44).

CLINICAL SCORING SYSTEMS

The diagnosis of HIT involves both clinical and laboratory components; thus, there are several proposed scoring systems to predict the likelihood of HIT by clinical characteristics. They include the HIT Expert Probability Score by Cuker et al. (36), a post-CPB scoring system by Lillo-Le Louët et al. (39), and the commonly used 4 T's scoring system by Warkentin et al. (45,46).