[Contemporary Reviews in Critical Care Medicine]

CHEST

Heparin-Induced Thrombocytopenia in the Patient Who Is Critically Ill

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Heparin-induced thrombocytopenia (HIT) is associated with clinically significant morbidity and mortality. Patients who are critically ill are commonly thrombocytopenic and exposed to heparin. Although HIT should be considered, it is not usually the cause of thrombocytopenia in the medical-surgical ICU population. A systematic approach to the patient who is critically ill who has thrombocytopenia according to clinical features, complemented by appropriate laboratory confirmation, should lead to a reduction in inappropriate laboratory testing and reduce the use of more expensive and less reliable anticoagulants. If the patient is deemed as being at intermediate or high risk for HIT or if HIT is confirmed by means of the serotonin-release assay, heparin should be stopped, heparin-bonded catheters should be removed, and a direct antithrombin or fondaparinux should be initiated to reduce the risk of thrombosis. Warfarin is absolutely contraindicated in the acute phase of HIT; if administered, its effects must be reversed by using vitamin K.

CHEST 2017; ■(■):■-■

KEY WORDS: critically ill; heparin; heparin-induced thrombocytopenia; thrombocytopenia; thrombosis

Heparin-induced thrombocytopenia (HIT) was described first in 1977,[1,2] 20 years after the first report of heparin-associated thrombosis.[3] Early recognition is important because of the high morbidity and mortality from arterial and venous thrombosis. It is caused by platelet-activating IgG antibodies binding the neoepitopes of platelet factor 4 (PF4)-heparin complexes, which originally were elucidated in 1992.[4,5] The diagnosis and treatment are particularly challenging in patients who are critically ill, owing to a high baseline prevalence of thrombocytopenia, risks for thrombosis from interruption in anticoagulation, or bleeding from the use of alternative anticoagulants in suspected or proven HIT. In this article, we provide an overview of HIT and an approach to diagnosis and treatment in patients who are critically ill, and we complement earlier reviews on this topic.[6-9]

Incidence

The incidence of HIT varies based on the patient population and type of heparin exposure, and it ranges from 1% to 5%[10] (Table 1).[11-19] Risk factors associated with HIT include undergoing surgery (OR,

ABBREVIATIONS: APTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; DOAC = direct oral anticoagulant; ECMO = extracorporeal membrane oxygenation; ELISA = enzyme-linked immunosorbent assay; FcγRIIA = Fc γ receptor IIA; HIT = heparin-induced thrombocytopenia; IVIg = IV immunoglobulin; LMWH = low-molecular-weight heparin; OD = optical density; PF4 = platelet factor 4; PROTECT = PROphylaxis for ThromboEmbolism in Critical Care Trial; SRA = serotonin-release assay; UFH = unfractionated heparin

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DOI: https://doi.org/10.1016/j.chest.2017.11.039

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REV 5.5.0 DTD ■ CHEST1472_proof ■ 8 January 2018 ■ 5:16 pm ■ EO: CHEST-17-0887

TABLE 1] Incidence of HIT as Reported in Registries, Clinical Trials, and Cohort Studies Q31

Study/Year	No. of Patients	Incidence (%)	Population at Risk
Warkentin et al[11]/2000	100	1.00	Cardiac
Cook et al[21]/2011	3,746	0.45	Medical-surgical ICU
Selleng et al[24]/2007	12,528	0.02	Medical-surgical ICU
Pouplard et al[12]/1999	263	3.42	Cardiac surgery for bypass
Walls et al[13]/1992	4,261	1.92	Cardiac surgery
Walls et al[14]/1992	764	4.58	Intra-aortic balloon pump
Singer et al[15]/1993	1,500	0.75	CABG, valve and combined
Ganzer et al[16]/1997	307	4.89	Orthopedic
Warkentin et al[17]/1995	332	2.41	Orthopedic elective hip
Leyvraz et al[18]/1991	204 205	2 with UFH 0 with LMWH	Orthopedic elective hip
Louridas[19]/1991	114	4.39	Vascular surgery

CABG = coronary artery bypass graft; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

3.25),[20] being female (OR, 2.37),[20] exposure to unfractionated heparin (UFH; 0.6%-2.6%) vs low-molecular-weight heparin (LMWH; 0.2%-0.3%)[21,22] (OR, 5.29),[20] and an elevated BMI. A BMI of 30 to 39 kg/m^2 with an OR of 2.94 (95% CI, 1.2-7.5) and a BMI > 40 kg/m^2 with an OR of 6.98 (95% CI, 1.6-28.2)[23] are associated with the development of HIT. Thrombocytopenia in patients who are critically ill is common Q11 and often leads physicians to consider HIT as a cause. However, HIT is not usually the culprit, and the incidence has been reported only at 0.02% to 0.45%.[24] A single-center German study of 12,528 patients reported an incidence of HIT of 0.21% in a medical-surgical ICU.[24] One of the largest prospective studies of the incidence of HIT was the HIT evaluation in critical care study embedded within the PROphylaxis for ThromboEmbolism in Critical Care Trial (PROTECT)[2,25]—a prospective evaluation of UFH vs LMWH (dalteparin) in 3,764 patients who were critically ill.[20] With use of the serotonin-release assay (SRA) to confirm the diagnosis, the overall incidence of HIT was 0.40%, or 0.53% with UFH and 0.26% with dalteparin. Within cardiac ICUs using UFH, this rate is substantially higher at 1% to 3%.[26,27]

Pathogenesis

HIT is a condition that results from the host production of platelet-activating IgG antibodies directed against heparin-platelet glycosaminoglycan and PF4 complexes Q12 that form following the exposure to heparin.[4,28] PF4 is a positively charged chemokine released from the alpha granules of activated platelets.[4] PF4 binds the negatively charged heparin anion in patients receiving either therapeutic or prophylactic doses of heparin.[28] Once ligated, these IgG antibodies cause cross-linkage of the platelet Fc γ receptor IIA (FcγRIIA).[29] This process in turn activates platelets,[29] leading to the release of platelet-derived microparticles that accelerate the thrombin formation and thrombotic complications of HIT.[30] The gene coding for FcγRIIA has two allotypes that differ in their ability to bind IgG immune complexes.[31] The 131R allotype was shown to confer a higher risk of thrombosis.[32] The authors of that study implicated the increased thrombotic risk to be related to an increase in cell activation by antibodies to PF4-heparin and a lower inhibitory effect of endogenous IgG (presumably owing to lower IgG2 binding of the 131R allotype). Typically, in a patient who is heparin naive, HIT-related thrombocytopenia occurs at least 5 days after heparin exposure because of the time required for primary antibody formation.[33,34] The risk for thrombosis may continue after platelet count recovery, and the binding of monocytes to PF4 to form antigenic complexes also has been implicated in thrombotic complications.[35,36]

Diagnosis

There are many clinical mimics of HIT, and the development of anti-PF4 antibodies does not always lead to HIT. Therefore, there are two requisites for the clinical diagnosis of HIT. First the patient must exhibit a clinical picture consistent with HIT, and second the patient's heparin-dependent antibodies must be platelet activating.

Clinical Features

The accurate diagnosis of HIT first requires recognition and understanding of its clinical manifestation. HIT's

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