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# Heparin-Induced Thrombocytopenia-Associated Thrombosis in Pediatric Intensive Care Patients

Markus Schmutz, MD\*; Lorenz Risch, MD†‡§; Andreas R. Huber, MD§; Anne Benn, MD||; and Joachim E. Fischer, MD, MSc||¶

**ABSTRACT.** *Background.* Heparin-induced thrombocytopenia (HIT), a well-known side effect of heparin therapy, occurs in 1% to 5% of adults exposed to heparin. Of those, about 29% to 88% develop thrombosis. Most data on HIT-associated thrombosis in children are confined to anecdotal reports.

*Objective.* To determine the incidence of HIT-associated thrombosis in heparin-exposed children.

*Methods.* We performed a retrospective cohort study on all patients admitted to our pediatric intensive care unit between August 1996 and January 1999. Patients who received heparin for  $\geq 5$  days were eligible. Within these patients, we identified all cases of radiologically confirmed thrombosis. Cases of thrombosis were reviewed for fulfillment of clinical HIT criteria. HIT-associated thrombosis was confirmed serologically by determination of levels of antibodies against heparin/platelet factor 4 complexes.

*Results.* Of 1950 children admitted during the study period, 612 were exposed to heparin for  $\geq 5$  days. Thrombosis occurred in 57 patients (9.3%). Plasma samples were available for 38 cases, of which 14 satisfied clinical HIT-criteria. Calculated incidence rate for HIT-associated thrombosis: 2.3%, (95% confidence interval: 1.3%–3.9%, for patients exposed to heparin  $\geq 5$  days). Nine patients suffered from venous, 2 patients from arterial, and 3 had combined arterial and venous thrombosis. None of the 14 patients died or underwent amputation. Six patients had heparin and platelet factor 4-complex antibody levels above the cutoff level for adults. The remaining 8 patients had significantly higher antibody levels than a matched control group.

*Conclusion.* Compared with that reported for adults, HIT-associated thrombosis in pediatric intensive care unit patients has a similar incidence but a less severe outcome. *Pediatrics* 2002;109(1). URL: <http://www.pediatrics.org/cgi/content/full/109/1/e10>; *heparin-induced thrombocytopenia, children, neonates, thrombosis.*

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ABBREVIATIONS. HIT, heparin-induced thrombocytopenia; HEPF4, heparin/platelet factor 4; PICU, pediatric intensive care unit; ELISA, enzyme-linked immunosorbent assay.

Heparin is the standard therapy for the prevention and the treatment of venous thromboembolism in adults and children. Immune-mediated, heparin-induced thrombocytopenia (HIT) is a well-known side effect of heparin therapy. HIT is one of the most frequent causes of drug-induced thrombocytopenia and can cause thrombosis. In adults, HIT occurs after heparin has been administered for at least 5 days. Patients with HIT present with a drop in their platelet count of  $\geq 50\%$ , often below  $150 \times 10^9/L$ .<sup>1–4</sup>

In the majority of patients, immune-mediated HIT is caused by antibodies against complexes of heparin/platelet factor 4 (HEPF4).<sup>3</sup> The antibody-HEPF4 complex binds to platelets via the platelet Fc  $\gamma$ -receptor IIA. It cross-links these receptors, thus ultimately activating platelets, leading to thrombosis and thrombocytopenia.<sup>5,6</sup> The antibody also activates endothelial cells by binding to surface heparin/platelet factor 4 complexes and as a result increases expression of tissue factor and generation of thrombin.<sup>7</sup>

The incidence of HIT in adults has been reported to be between 1% and 5%. Reported incidences depend on the type of heparin used and the population studied.<sup>2,8,9</sup> About 29% to 88% of adults with HIT develop arterial or venous thrombosis, with venous thrombosis being the more common complication.<sup>1,4,9,10</sup> HIT-induced thrombosis is associated with a high risk of mortality.<sup>9,10</sup> Although HIT occurs mainly in patients given therapeutic doses of heparin or systemic prophylaxis, it has also been reported in adults who were only exposed to heparin for “flushes” to maintain patency of intravenous lines,<sup>11</sup> and in patients previously sensitized with heparin-coated catheters only.<sup>12</sup> Although there are sufficient data regarding HIT and its thromboembolic complications in adults, little is known about the incidence of HIT in children.

HIT-associated thrombosis may develop particularly in critically ill pediatric patients and neonates who receive heparin for prevention and therapy of thrombosis or who are exposed to heparin for maintaining patency of vascular access. Most data on HIT in children are confined to case reports.<sup>13–17</sup> To date, only 1 prospective study has evaluated the incidence of HIT in newborns: Spadone et al<sup>18</sup> found an inci-

dence of 1%, and in this group, 85% developed umbilical or aortal thrombosis.

No systematic data exist on HIT-associated thrombosis in the at-risk population of critically ill infants and children. Therefore, we performed a retrospective cohort study to determine the incidence of HIT-associated thrombosis in a multidisciplinary pediatric intensive care unit (PICU).

### PATIENTS AND METHODS

The study was performed at a 19-bed multidisciplinary PICU, which serves as the tertiary referral center for eastern Switzerland. Reasons for admission comprised the entire spectrum of pediatric critical illness and included patients who had undergone cardiac and other major surgery. Patients in the PICU received unfractionated porcine heparin intravenously whenever central venous access was obtained, or arterial lines were placed, or for prophylaxis and treatment of thrombosis. Heparin-coated catheters were not used.

All patients admitted between August 1996 and January 1999 were eligible. Laboratory data and clinical data were available from the computerized data system of the PICU. In all patients, aliquots of plasma samples collected for routine purposes were stored at  $-80^{\circ}\text{C}$  within 6 hours from sample collection. The study was approved by the institutional review board, which waived the need for informed consent.

To identify patients with thrombosis and HIT, we first searched the database for all patients with thrombosis. A diagnosis of thrombosis required clinical symptoms plus the confirmation by Doppler-ultrasonography, angiography, or computed tomography scan. Each case of thrombosis was then reviewed for clinical HIT criteria: thrombocytopenia (platelet count below  $150 \times 10^9/\text{L}$ ) or drop of platelet count of  $>50\%$ , occurring after at least 5 days of heparin exposure.<sup>3</sup> Patients that had sepsis or other defined reasons for low platelet count or had received platelet transfusions were excluded.

For serologic confirmation of HIT, plasma samples from PICU patients, collected 1 to 36 hours after radiologic confirmation of thrombosis were tested for antibodies against HPF4 using a commercially available enzyme-linked immunosorbent assay (ELISA; Asserachrom, Diagnostica Stago, Asnières-sur-Seine, France). Optical densities are expressed as percent of the cutoff values for adults provided from the manufacturer. In adults, the diagnosis of HIT is regarded as serologically confirmed if HPF4 antibody levels exceed this cutoff.

Because pediatric specific cutoffs for the ELISA test are not available, we compared all identified pediatric HIT patients with thrombosis for whom plasma samples were available with a control group of 27 patients without clinical evidence of neither HIT nor thrombosis. With 1 exception, we were able to identify 2 matching control patients for each case of thrombosis. Controls were matched for age, diagnosis, intervention, duration of heparin administration, and sample storage time. Table 1 compares baseline characteristics for cases and controls. HPF4 antibody levels were compared between the two groups by a nonparametric test (Mann-Whitney *U* test).

**TABLE 1.** Characteristics of Patients With HIT and Thrombosis Compared With Controls (PICU Patients Without Clinical Evidence of HIT or Thrombosis)

Variable	HIT-Thrombosis	Controls
Number	14	27
Median age (mo; interquartile range)	6.5 (1–33)	4.3 (2–19)
Percentage of males	64%	59%
Heparin exposure before sample taken (d; mean, SD)	$14 \pm 10.5$	$15 \pm 9.5$
Storage time before analysis (mo; mean, SD)	$17 \pm 6.2$	$19.5 \pm 5.5$
Platelet count, mean (range) $\times 10^9/\text{L}$	58 (27–191)	336 (52–570)

SD indicates standard deviation.

### RESULTS

During the study period, 1950 children were admitted to the PICU (Fig 1). Of these, 612 had received heparin for  $>5$  days. Ninety patients with confirmed arterial and/or venous thrombosis were identified among all admitted patients. In 57 patients, thrombosis occurred after  $>5$  days of heparin. For 38 patients of the latter, plasma samples were available. Fourteen of these (37%) satisfied the clinical HIT criteria as defined above. The age of the 5 girls and 9 boys was 2 weeks to 13 years. Two patients suffered from isolated arterial thrombosis, whereas 9 patients experienced isolated venous thrombosis. Three patients had combined arterial and venous complications. Thrombocytopenia with a platelet count below  $150 \times 10^9/\text{L}$  occurred in 13 of these patients; the median platelet count nadir was  $58 \times 10^9/\text{L}$  (range:  $27\text{--}191 \times 10^9/\text{L}$ ). Thrombosis was diagnosed after a median of 10 days (range: 5–45 days) after onset of heparin administration.

Of the 14 patients with HIT, 6 patients had been exposed to heparin during previous hospitalizations for cardiac catheterization or major surgery. Eleven of the 14 patients with HIT-associated thrombosis had undergone cardiac surgery; this proportion reflects the distribution of admission diagnoses among patients who were exposed to heparin for  $\geq 5$  days in our institution. None of the patients died or needed limb amputation. Additional details of the patients with HIT-associated thrombosis are presented in Table 2.

Serologic confirmation of HIT using adult cutoff values was achieved in 6 patients. The remaining 8 patients also fulfilled the clinical criteria for HIT, but

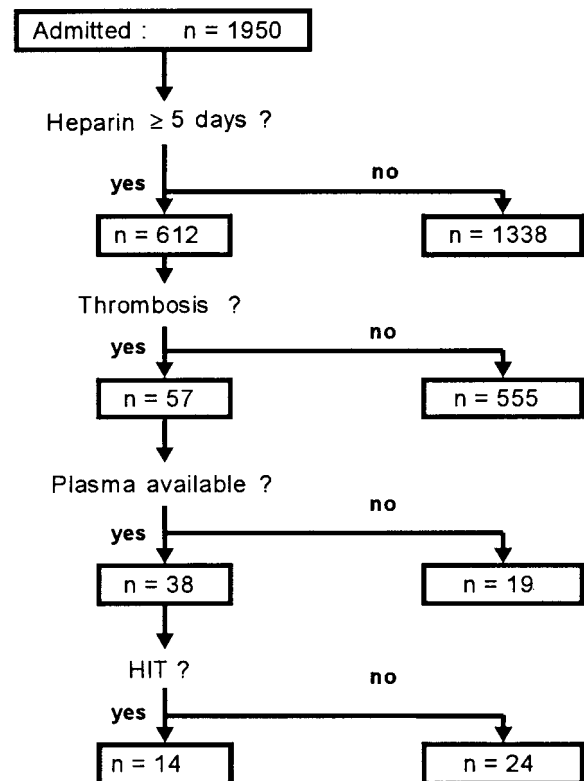


Fig 1. Flowchart of patient inclusion.

**TABLE 2.** Characteristics of 14 Patients With HIT-Associated Thrombosis

Gender, Age at Admission	Admission Diagnosis	Site of Thrombosis	Hep Exp	Previous Hep	Platelet Decline (%)	Platelet-Nadir × 10 <sup>9</sup> /L	HPF4-AB
Female, newborn	Open heart surgery	Left common iliac artery	6	No	51	191	153
Female, 6 mo	Open heart surgery	Right femoral artery; vena innominata	5	Yes	88	46	134
Male, 10 mo	Open heart surgery	Superior vena cava	10	Yes	55	46	112
Female, 15 mo	Open heart surgery	Right subclavian vein	16	Yes	65	123	104
Male, 13 y	Embolisation of aorto-pulmonary shunts after lung bleeding	Left subclavian vein; inferior vena cava; left and right external iliac veins	19	No	67	55	135
Male, 13 y	Meningococcal sepsis	Left external iliac vein	10	No	73	27	101
Male, newborn	Open heart surgery	Right external iliac vein	15	No	52	55	68
Male, 3 mo	Open heart surgery	Right femoral artery	7	Yes	56	37	54
Male, newborn	Open heart surgery	Right femoral artery; right femoral vein; superior vena cava; right renal vein	9	No	78	29	43
Female, newborn	Open heart surgery	Right subclavian vein	16	No	60	60	58
Male, 3 mo	Abdominal surgery	Inferior vena cava; left femoral vein	45	No	77	43	57
Male, 7 mo	Open heart surgery	Left external iliac vein	5	Yes	73	43	26
Male, 17 mo	Open heart surgery	Right internal iugular vein	25	Yes	61	80	83
Female, 4 y	Open heart surgery	Left external iugular vein	8	No	70	93	38

Hep Exp indicates heparin exposure before diagnosis (days); Previous Hep, heparin administration during preceding 6 months; HPF4-AB, percentage of adult cutoff value of ELISA optical density.

had antibody levels in the range of 26% to 80% of the cutoff for adults (Fig 2). Nevertheless, these 8 patients had significantly higher antibody levels than the controls ( $P = .004$ ).

Based on 612 exposed patients, the observed incidence of HIT-associated thrombosis was 2.3% (95%

confidence interval: 1.3%–3.9%). The proportion of thrombotic events attributed to HIT in patients exposed to heparin for  $\geq 5$  days amounted to 37% (95% confidence interval: 22%–54%, 14 of 38 patients).

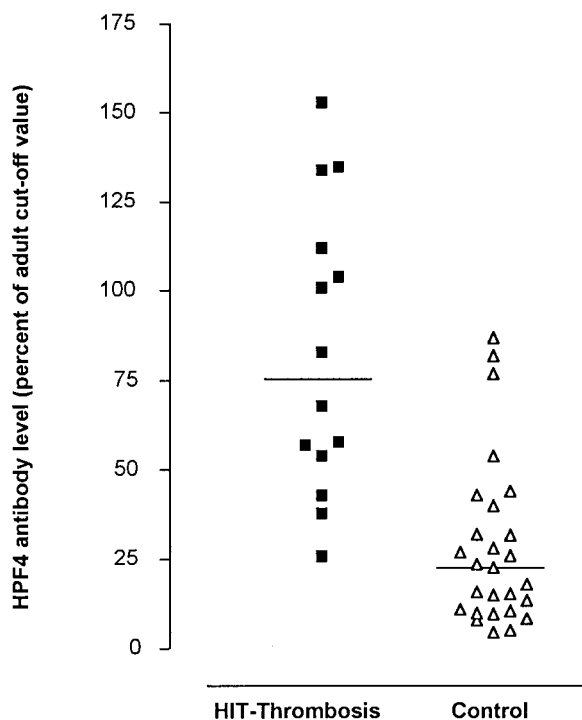
### DISCUSSION

This retrospective cohort study provides the first data on the incidence of HIT-associated thrombosis in an at-risk pediatric population. The calculated incidence in infants or children who are exposed to porcine heparin for 5 or more days was 2.3%. Our data indicate that the incidence of HIT-associated thrombosis in PICU patients is similar to that in adults.<sup>2,3,8,9</sup> It is possible that the true incidence in our PICU population was even higher, as we only included children with radiologically documented thromboembolism, and had to limit our analysis to those patients for whom plasma samples were available for serologic diagnosis (38 of 57).

We found a similar distribution of arterial and venous thromboses in the pediatric patients as reported for adults, but less severe outcomes.<sup>9,10</sup> One possible explanation is the preferential site of thrombosis. In our patients, all events occurred outside the pulmonary vascular bed, whereas in adults, HIT patients often present with pulmonary embolism.<sup>9</sup>

In this study, we used an ELISA for the determination of HPF4 antibodies. This ELISA has been established for diagnosis of HIT in adult patients and requires only minute amounts of sample.<sup>3,19</sup>

The majority of our patients with HIT-associated thrombosis were <1 year of age. During the first year of life, plasma levels of clotting factors as well as antibody production are lower than in adults.<sup>20–23</sup> Therefore, adult cutoff levels may not be applicable to young children. This is supported by the finding that only 6 patients with clinically suspected HIT-associated thrombosis had HPF4 antibody levels



**Fig 2.** HPF 4 antibody levels in patients with HIT and thrombosis ( $N = 14$ ) and controls ( $N = 27$ ). Data are presented as percent of cutoff optical density values for adults. The bar indicates the median value for each group. In 8 HIT-thrombosis patients with results below the cutoff for adults (100%), values were significantly higher than in controls ( $P = .004$ , Mann Whitney  $U$  test).

above the adult cutoff. However, the other 8 patients had significantly higher HPF4 antibody levels than their matched controls.

Several limitations of this study should be acknowledged. First, because of the design of this retrospective cohort study, we only included cases of thrombosis that were confirmed by radiology. Second, plasma was not available in all patients. In addition, minimizing iatrogenic blood loss is an imperative in neonatal and pediatric critical care; as a result, we were restrained to use plasma left over from daily routine requests. However, it is unlikely that a prospective study that would require informed consent for additional sampling for the purpose of HIT diagnosis would have attained a similar accrual rate of potentially eligible patients (38 of 57; 67%). Third, in adults the gold standard of serologic confirmation of HIT includes a functional test, ie, the [<sup>14</sup>C] serotonin release test.<sup>3</sup> Because of the design of the study, and because the functional assay has not been established for pediatric patients, we were unable to perform this test. However, in the presence of clinical criteria for HIT, a positive ELISA alone suffices for confirmation.<sup>3,24,25</sup> Overall, we believe these limitation do not invalidate our estimate of the incidence of HIT-associated thrombosis.

To establish a cutoff criterion for positive HPF4 antibody levels, a prospective cohort study in pediatric patients with both the ELISA and the functional test should be conducted. Such data are necessary to determine the incidence of HIT without thromboembolic complications. A prospective study should also elucidate the frequency and relevance of HPF4 antibodies in pediatric patients after cardiac surgery, a controversial issue in adult patients.<sup>8,26,27</sup> We conclude that physicians caring for children should be aware of HIT-associated thrombosis as a severe side effect of heparin administration. Critically ill newborns and children represent a high-risk group. Our retrospective analysis suggests that in these patients, HIT-associated thrombosis occurs at similar frequency as in adults. This syndrome may account for one third of all cases of thromboembolism during heparin administration. Clinicians may therefore consider reducing the use of unfractionated heparin for catheter flushing. In addition, we speculate that alternative anticoagulants (eg, low molecular weight heparin) may provide an opportunity to lower the incidence of HIT and HIT-associated thrombosis in pediatric patients. This, however, has to be substantiated in prospective, controlled trials.

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