

Heparin-Induced Thrombocytopenia in the Pediatric Population: A Review of Current Literature

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Heparin-induced thrombocytopenia is a rare and serious reaction to unfractionated heparin and low-molecular-weight heparins in children. Quick recognition, discontinuation of heparin, and subsequent treatment with an alternative anticoagulant are essential steps to prevent serious complications such as thrombus and limb amputation. The purpose of this review is to describe the clinical features of heparin-induced thrombocytopenia in children and to summarize the data available for its management. This paper summarizes data and relates the use of direct thrombin inhibitors with clinical outcomes. A literature search was conducted with Ovid, using the key terms *argatroban*, *bivalirudin*, *hirulog*, *danaparoid*, *lepirudin*, *direct thrombin inhibitor*, *heparin-induced thrombocytopenia*, *thrombosis*, *warfarin*, and *fondaparinux*. Articles were excluded if they were classified as editorials, review articles, or conference abstracts or if they involved patients 18 years of age or older or described disease states not related to thrombosis. Nineteen articles containing 33 case reports were identified and evaluated for this review. Of the 33 cases, 14, 10, 4, and 2 cases described the use of lepirudin, danaparoid, argatroban, and bivalirudin, respectively. Two cases did not report the type of anticoagulant used, and 1 case used aspirin. The most commonly reported complication was bleeding.

INDEX TERMS children, direct thrombin inhibitor, heparin-induced thrombocytopenia, low-molecular-weight heparin, unfractionated heparin

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INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a severe, life-threatening, immunological drug reaction that carries a high risk of morbidity and

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mortality. In the adult population, HIT affects approximately 5% of patients exposed to heparin.¹ In children, the frequency is reported to be 2.3% to 3.7% with a 1% to 3% prevalence in children undergoing cardiac surgery with the use of unfractionated heparin (UFH). The paucity of data available and the limited extent of reporting may be contributing to the low incidence. Nonetheless, the incidence in children is increasing, most likely due to increased awareness of the condition.^{2–9} The purpose of this review article is to describe the clinical features of HIT in

children and to summarize the data available for its treatment.

METHODS

A comprehensive literature search was performed using Medline (1950 to the second week of June 2010), International Pharmaceutical Abstracts (1970 to May 2010), and Embase (1980- 2010 Week 22). Keywords used in the search included *argatroban*, *bivalirudin*, *hirulog*, *danaparoid*, *lepirudin*, *direct thrombin inhibitor*, *heparin-induced thrombocytopenia*, *thrombosis*, *warfarin*, and *fondaparinux*. Search results were limited to children 17 years of age and younger, English language, and human. Inclusion criteria were studies with patients less than or equal to 17 years of age with a confirmed diagnosis of HIT and case reports. Exclusion criteria were patients 18 years of age or older, diseases not related to thrombosis, editorials, review articles, and conference abstracts.

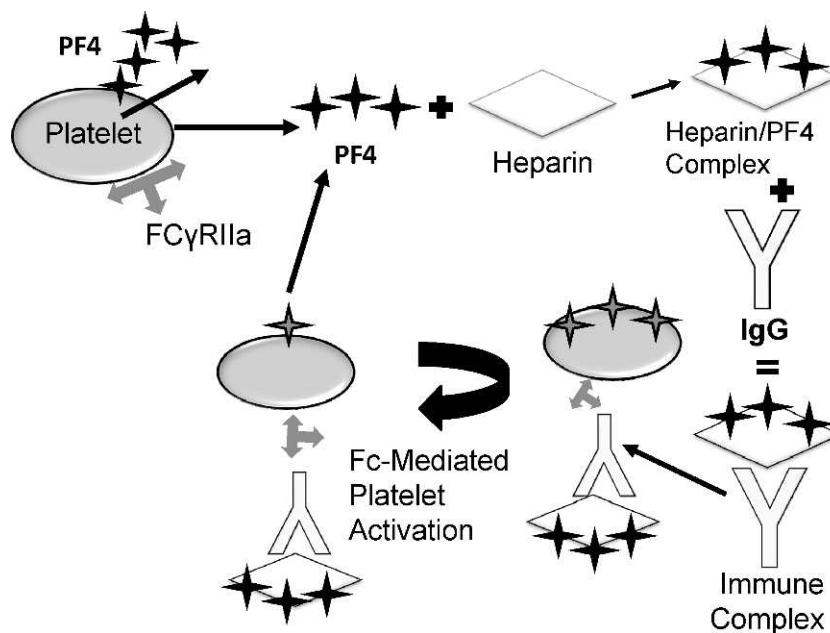


Figure. The pathophysiology of heparin-induced thrombocytopenia. FcγRIIa, Fc receptor; PF4, Platelet factor 4.

PATHOPHYSIOLOGY

HIT is immunological in nature and can occur after any exposure to heparin, including heparin flushes and heparin-coated catheters.^{10,11} UFH is often the anticoagulant of choice in children because of its efficacy, ease of monitoring, and reversibility, and clinical experience is extensive.¹² Thus, clinicians should be aware of how HIT occurs and that it can result as a serious consequence following the use of UFH.¹³

Pathologically, HIT results from the formation of antibodies against heparin, leading to platelet activation and consequent thrombin production.¹⁴ Platelet factor 4 (PF4) is a highly positive protein present in the α -granules of platelets. Following heparin exposure, PF4 quickly binds and neutralizes heparin. The PF4-heparin complex then serves as the primary antigen for antibodies, typically of the immunoglobulin G (IgG) class, which recognize and bind to exposed epitopes on PF4.^{15–21} The 3-component immune complex, composed of IgG, PF4, and heparin, then binds to and activates platelets via the Fc receptor (FcγRII). Following activation, platelets release more PF4 and other prothrombotic microparticles, propagating the cycle of platelet generation and thrombosis (Figure).^{22,23} Platelets then aggregate and are removed by the reticuloendothelial system, leading to thrombocytopenia.²⁴ Thrombocytopenia may also be explained by increased platelet consumption due

to extensive thrombosis.²⁵ Additionally, the antibody-antigen complex induces endothelial injury by binding to FcγRII receptors on monocytes, leading to tissue factor and thrombin production and promulgation.^{26,27} Therefore, thrombin plays a central role in the pathogenesis of HIT and represents a target for treatment via direct thrombin inhibitors (DTIs).^{22,28,29}

Other negatively charged polysaccharides or polyanions can bind to PF4 and induce conformational changes depending on the chain length and degree of sulfation.^{21,30} Because low-molecular-weight heparins (LMWH) are prepared from depolymerization of UFH, they bind weakly to PF4. This decreased affinity for PF4 may explain the lower antigenic potential of LMWH in causing HIT.^{31–35} The incidence of HIT in patients receiving LMWH is 1%, whereas with UFH it is estimated at 3% to 5%.^{34,36,37}

Risk Factors

The risk of children developing HIT is related to the extent of UFH exposure. Pediatric patients may receive UFH for various indications including prophylaxis and treatment of thromboembolic disorders, maintenance of indwelling arterial and venous cannulae, cardiac catheterization, cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), dialysis, and perioperative anticoagulation or in cases of anti-phospholipid and anticardiolipin antibodies or

protein S deficiency.³⁸⁻⁴¹ The greatest frequency of HIT has been reported in children with prolonged UFH exposure or those receiving larger cumulative doses of UFH.^{3,42}

In the pediatric population, a bimodal frequency for HIT occurrence is observed in neonates and adolescents, with its respective roles in cardiac surgery and umbilical lines or treatment of venous thromboembolism and surgery.^{42,43} In both populations, underlying thrombosis may additionally contribute to further thrombotic complications once HIT antibodies are formed.⁴⁴

Diagnosis

HIT may be observed following several clinical scenarios: when platelets decrease by more than 50% from baseline within 4 to 14 days after initiation of heparin; with or without the presence of thromboembolic complications or bleeding; or in the presence of heparin-dependent antibodies.^{2,13} Diagnosis is based on interpretation of clinical findings with laboratory confirmation of HIT antibodies.⁵ Diagnosis should be considered in light of recent platelet transfusion or differentiated against other causes of thrombocytopenia.⁴⁵⁻⁴⁹

The use of pretest probability scales can be helpful in determining the likelihood of HIT diagnosis. While no scale has been validated in children, the "4T" pretest probability scale developed by Warkentin and colleagues has been used in some pediatric institutions.^{51-53,86} With this scale, patients are assigned points based on the following criteria: thrombocytopenia, timing of platelet count fall or other sequelae, thrombosis or other complications, and other causes of thrombocytopenia. Points from each criterion are totaled and used to classify a patient as low, possible, or highly probable of positive HIT diagnosis (Table 1).^{53-55,86}

Laboratory Tests

While laboratory tests are supportive in the clinical diagnosis, neither functional nor serologic assays are 100% sensitive or specific because of their inherent design.^{25,57} Diagnosis is primarily clinical in approximately 20% of cases, and negative laboratory results do not exclude the diagnosis of HIT.⁵⁶⁻⁵⁸

Functional assays detect HIT based on the ability of the heparin-IgG-PF4 complex to activate platelets via Fc γ R2 receptors.⁵⁹⁻⁶² The serotonin release assay is considered the gold standard in HIT functional assays, based on high specificity and sensitivity results.^{64,65} However, a less sensitive assay (heparin-induced platelet aggregation test) was more commonly used in observed case reports.^{3,9,44,68-70}

While functional assays offer higher specificity and sensitivity, they are less sensitive than serologic assays. Serological or nonfunctional assays are immunological tests that detect antibody binding to PF4-heparin but not the ability of the complex to activate platelets. Those tests detect all subtypes of antibodies, including IgG, IgA, and IgM.⁵⁹⁻⁶⁰ Examples of serological assays include fluid-phase anti-PF4-heparin enzyme immunoassay, particle gel immunoassay, and enzyme-linked immunosorbent assay (ELISA).⁷⁰⁻⁷² The serological assay most commonly used in children is the ELISA test.^{43,48,68,69,74-83}

Immunoassays are available at most clinical laboratories and are technically less demanding than functional assays.^{6,84,85} Additional advantages include their increased sensitivity (>97%) compared to functional assays and the fact that results are unaffected by platelet or plasma factors.^{6,57,84,85} However, they have lower specificity in diagnosing HIT (74%-86%) as they detect antibody binding ability only. Because they detect HIT antibodies in patients who do not have thrombocytopenia or complications, the patients test positive in cases of both pathogenic and nonpathogenic HIT.^{6,12}

While the level of concordance between functional and immunological assays is high, 10% to 20% of cases have discordant results.⁶¹ A negative ELISA result generally rules out HIT. If the ELISA is positive, a functional assay may be performed to confirm diagnosis or to invalidate any chance of false positive with ELISA.^{84,86} Using a second assay following a negative functional or serological is especially important if the patient is at high risk for bleeding with a DTI or if clinical suspicion of HIT is low.⁵² The false-negative rate for both functional and antigen assays is approximately 5%.⁸⁷

Clinical Manifestations

Timing of Thrombocytopenia

The time to onset of thrombocytopenia, defined as a platelet count of less than $150 \times 10^9/L$, varies based on history of heparin exposure. In two-thirds of children with HIT, the platelet count begins to fall 5 to 10 days after heparin initiation and is known as typical onset.² In more than half of pediatric cases, children experienced a drop in platelets 5 to 15 days following initial therapy with UFH or enoxaparin.^{43,48,68,69,74,76,77,81,82,88} Conversely, some children may present with rapid-onset HIT. In this scenario, platelets decrease within minutes or hours of heparin initiation. This often occurs due to recent heparin exposure (within the last 100 days) that sensitizes the patient with residual and reactive HIT antibodies.^{57,89,90-92} Another small subset of patients may rarely

Table 1. Suggested Assessment Tool for Children with HIT^{51-55,86}

4 Ts	2 Points	1 Point	0 Points
Thrombocytopenia	>50% platelet fall and platelet nadir of $\geq 20 \times 10^9/L$ and no surgery within the preceding 3 days	>50% platelet fall but surgery within preceding 3 days or Any combination of platelet fall and platelet nadir that does not meet criteria for a score of 2 points or a score of 0 points	<30% platelet fall or Any platelet nadir $< 10 \times 10^9/L$
Timing of platelet count or thrombosis	Platelets fall 5-10 day after start of heparin or Platelet fall within 1 day of start of heparin and exposure to heparin within the past 5-30 days	Onset unclear or Platelet fall after day 10 or Platelet fall within <1 day of starting heparin (if exposed to heparin within the past 30-100 days)	Platelet fall within <4 days without exposure to heparin in the past 100 days
Thrombosis or other sequelae	Confirmed new thrombosis or Skin necrosis at injection site or Anaphylactoid reaction to IV heparin bolus; Adrenal hemorrhage	Progressive or recurrent venous thrombosis or Suspected thrombosis or Red skin lesions at heparin injection site	Thrombosis not suspected
Other causes of thrombocytopenia	No other cause is evident	Possible other cause is evident	Probable other cause is present

IV, intravenous

experience delayed-onset HIT, which is observed days after heparin has been discontinued. This atypical presentation validates the autoimmune nature of HIT, demonstrating that PF4/heparin-reactive antibodies can activate platelets even in the absence of heparin.^{93–95}

Characteristics of Thrombocytopenia

Platelet counts greater than $150 \times 10^9/L$ have been observed in children with HIT.³⁵ Because the individual platelet count may vary, a more accurate indicator of HIT is a decrease of $>50\%$ in platelet count from baseline.^{34,96,97} Usually, platelet counts fall to a nadir of $50 \times 10^9/L$, although for 10% of children, their lowest platelet count is reached while it is still in the normal range.⁴²

Thrombosis and Other Complications

In children, a new thromboembolic complication (TEC) may be the first presenting symptom of HIT. In all pediatric cases identified, at least one TEC was observed prior to HIT diagnosis.^{3,9,43,44,48,68–70,74–83,98,99} Studies in humans suggest that the thrombotic risk is higher in patient with higher levels of PF4-heparin antibody.¹⁰⁰ While the thromboembolic events may be arterial or venous in origin, venous thromboses are more commonly observed and include thrombi in the subclavian and femoral veins.^{42,97} Pulmonary embolism, a common complication in adult patients with HIT, is rarely seen in young children (<12 years old).³

HIT should be suspected in children with normal platelet counts suffering from unexplained thrombosis.⁴² In those cases, early recognition of HIT is essential, as thromboembolism can result in loss of limb, myocardial infarction, stroke, and death.¹⁰¹ However, bleeding is a relatively rare complication in children and adults with HIT.^{4,42} Other rare complications include acute thoracic pain, respiratory distress, anaphylactic shock, prolonged fever.^{42,43,102} Symptoms observed in adults that have not yet been reported in children include cerebral venous thrombosis, adrenal infarction, and transient global amnesia.^{42,97}

PHARMACOTHERAPY

Direct Thrombin Inhibitors

Direct thrombin inhibitors bind to 3 active sites and 2 exosites on thrombin and inhibit fibrin formation. Exosite 1 serves primarily as a dock for fibrin, while exosite 2 allows for heparin binding.¹⁰³ Based on the DTI's affinity for either the active site or exosite 1, it may be classified as bivalent or univalent. Bivalent DTIs bind with equal affinity to the active site and exosite and

include lepirudin (Refludan; Bayer Healthcare Pharmaceuticals, Robinson, PA) and bivalirudin (Angiomax; The Medicines Company, Parsippany, NJ). Univalent agents bind only to the active site and include argatroban (Novastan; GlaxoSmith-Kline, Zebulon, NC).¹⁰⁴ Because DTIs act independently of antithrombin, they have an enhanced capacity to inhibit thrombin bound to fibrin, offering a unique advantage over heparins.^{105–107} Additionally, they do not bind to plasma proteins, offering a more predictable response over UFH and greater efficacy than LMWH.¹⁰⁸ DTIs also possess antiplatelet effects due to thrombin's role in platelet activation.^{109,110}

Lepirudin

Lepirudin is approved by the US Food and Drug Administration (FDA) for anticoagulation in adult patients with HIT and associated thromboembolic disease to prevent further TEC (Table 2).¹¹⁰ However, its safety and efficacy have not been established in children. Lepirudin is a recombinant protein analog of the leech hirudin protein. It is highly specific in its ability to irreversibly bind to both the catalytic and enzymatic sites of thrombin.^{110–112} Mechanistically, 1 molecule of lepirudin forms a tight complex with 1 molecule of thrombin, neutralizing the actions of thrombin, including those molecules already entrapped in clots.¹¹² Lepirudin is eliminated renally and requires dose modification in patients with renal insufficiency or dialysis. Approximately 50% of a lepirudin dose is excreted in the urine and most of it remains unchanged. Lepirudin follows a 2-compartment model with an initial distributive half-life of 10 minutes and an elimination half-life of 80 minutes.¹¹⁰

Lepirudin is monitored every 4 hours, based on its terminal half-life, using activated partial thromboplastin time (aPTT) (Table 2).^{5,110} Similar to other agents in its class, lepirudin does not interact with HIT antibodies. However, in 30% of patients, antibodies develop against lepirudin after the first exposure and in 70% of patients upon second exposure. Severe and in some cases fatal reactions have been reported following lepirudin sensitization. For this reason, lepirudin should be used only once during a patient's lifetime.^{5,110} As a result of antibody formation, renal clearance of lepirudin is delayed, leading to accumulation, which may place the patient at increased risk of bleeding.¹¹³ Among the DTIs, the incidence of bleeding is highest with lepirudin, at approximately 17% in patients receiving therapeutic doses. Lepirudin antibodies also display cross-sensitivity to bivalirudin. Therefore, it

Table 2. Pharmacokinetic Profiles of Anticoagulants Used in HIT ^{58,96,107,110,112,116}

Class	Lepirudin (Refludan)	Argatroban (Novastan)	Bivalirudin (Angiomax)	Danaparoid (Orgaran)
Mechanism	Direct thrombin inhibitor	Direct thrombin inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor
FDA-approved indications	Prophylaxis or treatment of thrombosis in patients with HIT	Prophylaxis or treatment of thrombosis in patients with HIT; Anticoagulant in patients with or at risk of HIT undergoing PCI	Anticoagulant in patients with or at risk of HIT undergoing PCI	Withdrawn from US market in 2002
Administration	Intravenous or subcutaneous	Intravenous	Intravenous or subcutaneous*	Intravenous or subcutaneous
Distribution	Extracellular fluid; Protein binding not characterized	Extracellular fluid; 54% protein binding	No protein binding	Protein binding not characterized
Metabolism	Renal	Hepatic	Renal and proteolytic	Renal
Elimination half-life	80 min	30-50 min	25 min	18-28 hr
Monitoring	ECT, [†] aPTT; aPTT: 1.5-2.5 times patient's baseline or mean of laboratory normal range	ECT, [†] aPTT; aPTT: 1.5-3 times patient's baseline or mean of laboratory normal range	ACT, [†] aPTT; ACT: 300-350 sec during procedure	Not regularly required; Anti-factor Xa levels should be monitored during renal insufficiency, 0.5-0.8 units/mL
Antidote	None	None	None	None

ACT, activated clotting time; aPTT, activated partial thromboplastin time; ECT, ecarin clotting time; HIT, heparin induced thrombocytopenia; PCI, percutaneous coronary intervention

* Non-FDA approved

[†] Preferred method of monitoring

is recommended that bivalirudin be avoided in patients who previously received lepirudin.¹¹²

Lepirudin is typically administered intravenously for HIT management; however, subcutaneous administration without a bolus dose has also been reported in a few instances.¹¹⁴ For example, a patient with a history of HIT who is not able to tolerate warfarin would not be a candidate for bridge therapy from intravenous (IV) lepirudin to warfarin. In this patient, bridging therapy to subcutaneous lepirudin may be an option.¹¹⁵

Of the 33 pediatric HIT cases reported in the literature, lepirudin was used in 14 of them (Table 3).^{3,9,43,48,68,70,74,78,79,81,82} In 6 of those cases, 14 children were male and 7 were female; 1 case did not report the gender of the child. Children ranged in age from 28 weeks to 17 years. Indications for anticoagulation included spontaneous deep vein thrombosis (DVT), thrombus following various cardiac surgeries, cardiac catheterization, and ECMO. Patient's concomitant medications were not mentioned in any of the cases. Bolus doses ranged from 0.25 to 0.4 mg/kg, compared to the usual adult bolus dose of 0.4 mg/kg. Starting infusion rates were reported in 6 of the 14 cases and ranged from 0.0055 to 0.15 mg/kg/hr compared to an adult infusion rate of 0.15 mg/kg/hr.

Bleeding outcomes were reported in 10 of these 14 cases.^{3,68,78,79,81} Three of these 10 cases were positive for a bleeding complication, while the other 7 reported no bleeding complications. The first case with bleeding complications included an 11-year-old female who was diagnosed with HIT following anticoagulation with UFH for treatment of DVT in the pelvis and leg.³ The patient experienced hematuria while receiving lepirudin; however, the bolus dose and rate of infusion were not reported.

The second patient, a 4-year-old female weighing 12 kg, received a 4.8-mg loading dose (0.4 mg/kg) and 3.37-mg priming dose (0.28 mg/kg) of lepirudin following a newly discovered clot in the ECMO circuit.⁶⁸ Three days prior to starting ECMO, the patient was diagnosed with HIT using supported by the use of PF4-heparin antibody assay. Despite this diagnosis, the ECMO circuit was primed and maintained using heparin, which resulted in clot formation and platelet drop within 24 hours. While no bleeding and thrombolytic complications were reported while using lepirudin, postoperative bleeding was not well controlled. The patient died 5 days after heart transplantation.

The third patient, a 4-month-old patient weighing 5.7 kg, lost 50 mL of blood during a surgical procedure using lepirudin boluses of 0.25 mg/kg and infusion doses of 0.04 mg/kg/hr, initially with a continuing dose of 0.08 mg/kg/hr for use during CPB.⁷⁹ The patient had been identified as HIT-

positive during a previous hospitalization at which time she underwent a cardiac procedure using heparin. During the second hospitalization, this patient underwent a bidirectional Glenn shunt procedure. In anticipation of CPB, an infusion of lepirudin was initiated. A bolus dose for the procedure was 0.25 mg/kg, followed by another bolus of 0.25 mg/kg 25 minutes later. Starting and continuing infusions were 0.08 mg/kg/hr. Monitoring using aPTT was done at baseline and 10 minutes following each bolus dose. Values were reported at 51.9, 83.1, and 105.2 seconds, respectively, with a normal reference value of 25 seconds. The higher aPTT values were anticipated in the vascular surgery; however, lepirudin infusion was stopped for 1 hour following the procedure to allow the aPTT value to decrease to the preoperative therapeutic range.

In most cases, thrombolytic complications directly resulting from the use of lepirudin were not reported.^{3,9,43,68,70,78,78,81} One case, however, discussed a probable DVT well after lepirudin had been discontinued.⁸ A 21-month-old male patient with a history of hypoplastic left heart syndrome experienced decreasing platelet counts over 7 days despite transfusion, and test results indicated the presence of HIT antibodies. Heparin was discontinued on the eighth day following surgery, and lepirudin was initiated as a 0.2 mg/kg bolus dose, followed by an infusion at 0.1 mg/kg/hr and was adjusted to maintain the aPTT at 1.5 to 2 times the baseline value. Suspicious thrombus formation was discovered upon echocardiogram 24 days after surgery and 8 days after lepirudin had been discontinued. While computed topography scans suggested thrombus formation in extracardiac conduit and probable DVT in the right femoral and external iliac vein, warfarin was continued for 26 more days. The aPTT value before discontinuation of lepirudin was therapeutic, 45 to 60 seconds (1.5-2 times baseline aPTT), and the infusion rate was decreased to 0.08 mg/kg/hour 1 day before the drug's discontinuation due to decreased renal function.

In two case reports, lepirudin was used during surgical procedures.^{9,78} In the first case, lepirudin was used for extracorporeal circulation (ECC) priming and prior to ECC initiation with bolus doses of 0.2 mg/kg and 0.25 mg/kg, respectively.⁹ The infusion dose was maintained to keep blood concentrations between 3.5 and 5 mg/L and was discontinued 30 minutes prior to ECC termination. No bleeding or thrombotic complications resulting from lepirudin or surgery were discussed. In the second case, lepirudin was used prior to, during, and after a bidirectional Glenn shunt procedure.⁷⁸ While the duration of therapy was variable in these

Table 3. Anticoagulants and Bleeding Complications in Selected Case Reports

Study (Population)	Anticoagulant	Dosage	Bleeding	Thrombotic Events
Hanke et al ⁷⁴ (n=1)	Lepirudin	Starting dosage: 5.5 mcg/kg/hr Maximum dosage: 46 mcg/kg/hr	0	0
Schmitz et al ⁷⁵ (n=1)	Argatroban	Starting dosage: 2 mcg/kg/min Infusion range: 1-2.3 mcg/kg/min	0	None reported
Maurer et al ⁷⁶ (n=1)	Argatroban	Starting dosage: 2 mcg/kg/min Adjusted to 0.32-0.4 mcg/kg/min Continued at 0.4-7.9 mcg/kg/min upon tPA discontinuation	0	Yes, mild post-thrombotic syndrome
Almond et al ⁷⁷ (n=1)	Bivalirudin	Bypass circuit primer: 50 mg Cardiopulmonary bypass: IV bolus, 0.15 mg/kg Continuous infusion: 0.25 mg/kg/hr	Significant	None reported
Böning et al ⁹ (n=4)	Argatroban Lepirudin	Venoarterial ECMO: 2 mcg/kg/min without bolus ECC priming: 0.2 mg/kg	0 0	None reported None reported

Table 3. Continued.

Study (Population)	Anticoagulant	Dosage	Bleeding	Thrombotic Events
Klenner et al ³ (n=12)	Danaparoid	Pre-ECC initiation: 0.25 mg/kg Dose adjusted to maintain blood concentration: 3.5-5 3.5 µg/mL Discontinued 30 min prior to ECC termination	None reported	None reported
	Danaparoid		None reported	
	Lepirudin		None reported	
	Lepirudin		Yes, hematuria	
	Not reported		None reported	
	Danaparoid		None reported	
	Danaparoid		None reported	
	Aspirin		None reported	
	Lepirudin		None reported	
	Dager et al ⁷⁸ (n=1)	Lepirudin	Bolus: 0.1 mg/kg Starting dosage: 0.12 mg/kg/hr	0
Dager and White ⁴⁸ (n=1)	Lepirudin	Starting dosage: 0.1 mg/kg/hr Titrated to 0.13 mg/kg/hr	0	0
	Lepirudin	Bolus: 0.4 mg/kg Starting dosage: 0.15 mg/kg/hr	0	None reported
Dietcher et al ⁶⁸ (n=2)	Lepirudin	Bolus: 0.4 mg/kg	Yes	0
	Lepirudin	Bolus: 0.4 mg/kg	Yes	0

Table 3. Continued.

Study (Population)	Anticoagulant	Dosage	Bleeding	Thrombotic Events
Zohrer et al ⁶⁹ (n=4)	Danaparoid	Infusion range: 1.2 –3.4 unit/kg/hr	0	newly formed DVT of left lower leg
	Danaparoid	Bolus: 20.8 unit/kg Infusion range: 2.7-4.2 units/kg/hr	0	None reported
	Danaparoid	Infusion range: 2.7-5.4 unit/kg/hr	0	None reported
	Danaparoid	Bolus: 28.6 unit/kg Infusion range: 2.9-7.1 unit/kg/hr	0	0
Severin and Sutor ⁴³ (n=31)	Lepirudin	Not reported	None reported	None reported
Ranze et al ⁴⁴ (n=23)	Danaparoid	Not reported	0	None reported
Iannoli et al ⁷⁹ (n=1)	Lepirudin	Pre-cardiopulmonary bypass: 0.04 mg/kg/hr Bolus: 0.25 mg/kg Starting infusion: 0.08 mg/kg/hr 2 nd bolus(25 minutes later): 0.25 mg/kg Continuing infusion: 0.08 mg/kg/hy	Yes (50 mL during procedure) None reported postoperatively	None reported
Saxon et al ⁸⁰ (n=1)	Danaparoid	Bolus: 30 units/kg Starting infusion: 2 units/kg/hr	Yes. Portion of postoperative bleeding attributed to danaparoid use	0
Breinholt et al ⁸⁷ (n=1)	Bivalirudin	Bolus: 0.75 mg/kg Starting infusion: 0.75 mg/kg/hr	0	None reported
John and Hallisey ⁸¹ (n=1)	Lepirudin	0.15 mg/kg/hr	None reported	None reported

Table 3. Continued.

Study (Population)	Anticoagulant	Dosage	Bleeding	Thrombotic Events
Knoderer et al ⁸² (n=1)	Lepirudin	Bolus: 0.2 mg/kg Starting infusion: 0.1 mg/kg/hr 7 days post-bolus: 0.08 mg/hr	0	Yes, probably DVT
Frost et al. ⁸³ (n=2)	None reported	Not available	0	0
	Argatroban	Administered at DVT treatment dosages	None reported	None reported
Nguyen et al ⁷⁰ (n=1)	Lepirudin	Bolus: 0.2 mg/kg Starting infusion: 0.1 mg/kg/hr to target Continuing infusion: 0.03-0.05 mg/kg/hr	0	None reported

DVT, deep vein thrombosis; ECC, extracorporeal circulation; ECMO, extracorporeal membrane oxygenation; IV, intravenous; tPA, tissue plasminogen activator

two case reports, patients were treated for an average length of 9 days.^{9,78}

Extended use of lepirudin was described by Hanke and colleagues⁷⁴ in a 6-year-old patient who went through a surgical intervention for tetralogy of Fallot using UFH. Two days after surgery, the patient began receiving continuous renal replacement therapy (CRRT). Seven days after surgery, an ELISA for heparin-induced antibodies was positive. Anticoagulation therapy was changed to lepirudin, and monitoring was performed using the ecarin clotting time test with a target range of 0.1 to 0.2 mg/L. The only reported complication occurred 12 days after the patient began lepirudin when platelet transfusion led to a catheter-related thrombosis and increased D-dimer. Consequently, CRRT was discontinued, the patient's platelet count improved steadily, and lepirudin was continued successfully for a total of 6 weeks.

Argatroban

Argatroban is FDA approved for prophylaxis and treatment of thrombosis in adult patients with HIT. It is also used as an adjunct therapy for percutaneous coronary intervention (PCI) in patients who have or are at risk for thrombosis due to HIT (Table 2). Argatroban is a small molecule synthetic compound derived from L-arginine that binds selectively and reversibly to the catalytic site of thrombin, competitively inhibiting the action of thrombin, including fibrin generation and platelet aggregation.^{111,112} Following intravenous administration, the volume of distribution of argatroban in healthy subjects is 180 mL/kg, with a half-life of 30 to 50 minutes. Unlike lepirudin, argatroban is cleared hepatically and excreted in bile and must be dose-adjusted in liver dysfunction.¹¹⁶ Bleeding with argatroban has been reported in 6% to 7% of adult and child patients. Contrary to the mechanism of lepirudin, the development of antibodies against argatroban has not been reported.¹¹² Additionally, argatroban falsely increases International Normalized Ratio (INR) value. While all DTIs have the ability to inaccurately increase INR values, argatroban has the greatest tendency to do so because of the high molar concentrations of argatroban required to achieve thrombin inhibition. In vitro, this results in greater thrombin inhibition and, subsequently, higher prothrombin values. While this interaction constitutes a drug-laboratory and not a pharmacodynamic interaction, it is of particular importance when transitioning to warfarin therapy.^{117,118}

Children treated with argatroban ranged in age between 2 months and 15 years.^{75-77,83} Two children were female and the other 2 were male.

Indications of anticoagulation with heparin included flushing of central catheter, DVT prophylaxis and treatment, bilateral pulmonary embolism treatment, left-ventricular assist device (LVAD) placement, ECMO, and CPB. Concomitant medications were not discussed in any of the cases; however, in the case of a 15-year-old male with Gitelman syndrome, the patient had received digoxin, furosemide, captopril, and aspirin at home.⁷⁵ As his condition worsened, milrinone was also added to his medication regimen. In the 4 cases that used argatroban, the starting infusion rate was 2 mcg/kg/min without a bolus dose, similar to the recommended dose used in the adult population.^{75-77,83} Continuing doses were adjusted based on aPTT values and administered at a wide range of doses (0.32-8 mcg/kg/min)

In 2 pediatric HIT cases, argatroban was used after an alternative anticoagulant failed.^{76,77} The first case report was in a previously healthy, obese 11-year-old 68-kg female treated for lobar pneumonia.⁷⁶ Immobilization, obesity, and May-Thurner syndrome contributed to development of DVT and bilateral pulmonary emboli, which were successfully treated with heparin. Sixteen days later, the patient experienced recurrent DVT in both legs, and ELISA results were reported positive. Consequently, bivalirudin was initiated at a 125 mcg/kg bolus, followed by 125 mcg/kg/hr infusion to maintain an aPTT goal of 1.5 to 2 times baseline. However, 12 days after the patient began taking bivalirudin, rethrombosis occurred, and site-directed alteplase was used concurrently for 12 days to successfully lyse the clot. Because of renal compromise, argatroban was initiated at 2 mcg/kg/min. Nineteen days later, therapy with argatroban was switched to fondaparinux, 7.5 mg daily, in preparation for discharge. The patient, however, experienced recurrent pulmonary emboli and bilateral vein occlusion upon transition to fondaparinux. Argatroban at infusion rates of up to 17.5 mcg/kg/hr and alteplase were used. After 3 months in the hospital, the patient was transitioned from argatroban to warfarin and discharged on warfarin for 21 more days.

In the second case, a 5-year-old female heart transplant patient was on ECMO for 14 days before being diagnosed with HIT.⁷⁷ When a donor heart became available, bivalirudin was used during CPB. Significant bleeding occurred once CPB was discontinued. Following the bleed, argatroban was resumed at 2 mcg/kg/min and continued until her transfer to a different ward, 33 days later.

In the 2 remaining cases, argatroban was used as the primary anticoagulant following diagnosis of HIT. The first case, described by Schmitz and colleagues,⁷⁵ involved a 15-year-old male with

Gitelman syndrome and asthma, in which heparin was used as thromboprophylaxis for 4 weeks. An LVAD was placed using additional heparin bolus and infusion doses. In addition, heparin flushes were used to maintain patency of a central catheter. However, heparin was discontinued shortly thereafter when the ELISA result came back positive. Warfarin and argatroban were started 24 hours after LVAD placement. Two days later, warfarin was gradually increased as argatroban was decreased while targeting an INR value of 3. Argatroban was discontinued 17 days postoperatively, and the patient was continued on warfarin, aspirin, and dipyridamole.

The remaining case discussed a 37-week-old gestational age male infant with a diagnosis of primary pulmonary hypertension and seizure disorder.⁸³ A total of 200 units of heparin were used during the patient's first 10 days of life. At 2 months of age, a routine check-up revealed a platelet count of 21,000, and the patient was admitted for anemia, thrombocytopenia, and infection soon after. A central line was flushed with 10 units of heparin. Eight days after admission, the patient experienced a DVT that was treated with heparin. Further testing revealed positive heparin antibodies. Heparin was immediately discontinued, and argatroban therapy was initiated at 2 mcg/kg/min. Later, argatroban was used for tricuspid valve excision, although the doses during the procedure were not reported. None of the patients receiving argatroban experienced bleeding. One patient, however, experienced mild post-thrombotic syndrome which was not described further by the authors.⁷⁵

Bivalirudin

Bivalirudin is FDA approved for anticoagulation in adult patients undergoing PCI with or at risk of HIT or heparin-induced thrombocytopenia-thrombosis syndrome. Like other DTIs, bivalirudin is not approved in children. A molecule of this 20 amino acid polypeptide binds bivalently to thrombin, inhibiting its immediate and downstream actions. Unlike lepirudin, bivalirudin offers only transient thrombin inhibition; once bound, bivalirudin is cleaved by thrombin, which restores thrombin's function.¹⁰⁷ Bivalirudin may be administered intravenously or subcutaneously, although the latter is not FDA-approved.

Bivalirudin displays linear pharmacokinetics and is eliminated from plasma by a combination of renal and enzymatic mechanisms. Because 80% of the drug's metabolism occurs through proteolytic enzymes, bivalirudin offers a unique advantage in patients who experience renal and/or hepatic insufficiency. In a study by Steinberg,¹¹⁹ 115

patients were examined for effects of renal function on bleeding risk from bivalirudin. Patients with creatinine clearance less than 60 mL/min were approximately 3.3 times more likely to experience bleeding complication than those with creatinine clearance greater than 60 mL/min.¹¹⁹ Elimination half-life of this agent is the shortest of all direct thrombin inhibitors, at approximately 25 minutes in patients with normal renal function. Bleeding incidence is approximately 2.4% in patients undergoing PCI with a history of HIT.¹⁰⁷ Despite its metabolism, bivalirudin doses should be decreased in cases of moderate and severe renal dysfunction to protect the patient from over-anticoagulation.

Bivalirudin use was reported in two cases. Almond and colleagues⁷⁷ reported using a 50-mg loading dose and a 0.15 mg/kg bolus for bypass circuit primer and CPB, respectively, followed by an intravenous infusion of 0.25 mg/kg/hr in a 5-year-old female (weight unknown). Repeat bolus doses were administered, and the infusion rate was titrated to maintain activated clotting time >400 seconds over the next first 30 minutes of therapy. The patient experienced significant bleeding following separation from bypass, although the parameters qualifying the bleed as significant were not provided. While the causality between bivalirudin and bleeding incidence was not clear, bleeding resolved in 12 hours with the administration of fresh-frozen plasma, recombinant Factor VIIa, and ultrafiltration. No thrombotic complications were reported.

In the second case report, a bolus dose of 0.75 mg/kg, followed by a starting infusion of 0.75 mg/kg/hr for cardiac catheterization was used in a 2-year-old boy with complex congenital heart disease. The patient had been diagnosed with HIT following a bidirectional Glenn procedure at 6 months of age.⁸⁷ Unlike the first case, bivalirudin did not result in bleeding complications. Thrombotic complications as a result of bivalirudin were reported in either case (Table 3).^{77,87}

Danaparoid

Danaparoid (Orgaran; Schering-Plough Corp., Memphis, TN), while not FDA approved for HIT in either adults or children in the United States (US), has been used in other countries.¹¹¹ Danaparoid was voluntarily withdrawn from the US market in 2002 with the introduction of fondaparinux. It is a low-molecular-weight heparinoid consisting of a mixture of heparin, dermatan, and chondroitin sulfates. Derived from porcine gut mucosa, danaparoid selectively inhibits Factor Xa, similar to the actions of fondaparinux. Unlike the direct thrombin inhibitors, danaparoid may be

administered subcutaneously or intravenously and possesses a long half-life, ranging from 18-28 hours.¹²⁰ Danaparoid is renally cleared and requires dose adjustment in renal dysfunction. While routine monitoring is not required, anti-factor Xa levels may be assessed in patients with renal failure, dialysis, or in body habitus extremes. Incidence of bleeding has been reported at approximately 8% in the general population.¹¹²

Danaparoid was used in 10 of the 33 identified case reports. Three cases reported use of bolus doses, ranging from 20 to 30 units/kg.^{69,80} Infusion rates were variable and ranged from 2 to 7.1 units/kg/hr.⁶⁹⁻⁸⁰ In most cases, danaparoid did not result in bleeding complications; however, Saxon and colleagues attributed a portion of postoperative bleeding to the use of danaparoid.⁸⁰ One case report, described by Zohrer and colleagues,⁶⁹ resulted in a complication of thromboembolic origin; the patient had a newly formed DVT in the left lower leg. Cross-sensitivity to heparin antibodies was suspected, and danaparoid was replaced with hirudin for 2 days with no further progression of the thrombus (Table 3).

DISCUSSION

Summary of Findings

This review summarizes the most recent case reports of HIT in children, with a focus on available anticoagulants and associated complications. Earlier reviews have focused on identifying age groups in which HIT is most commonly observed or identifying differences in clinical presentation; however, they have not focused on doses used in available cases. Previous literature has focused on determining the frequency of DTI and Factor Xa inhibitor use or risk factors for HIT in children.

Pediatric patients exposed to heparin are at risk for side effects and complications, including HIT. Based on the limited number of case reports available, the occurrence of HIT in children appears rare. However, the true incidence of HIT is unknown, as all cases of HIT in children may not have been reported and/or published. In most cases, the offending agent in identified pediatric patients was UFH; in 1 case, the agent was enoxaparin. Current data in children do not compare incidence rates of HIT with heparin versus LMWH. Furthermore, prospective clinical trials do not currently exist to offer guidance on the diagnosis and management of this condition in children. Most patients are successfully treated with one of these agents. In two cases, failure with bivalirudin and fondaparinux prompted the use of argatroban.

The demographics of the children in these cases are diverse, with higher incidence in neonates and

adolescents. The cases represent myriad ages and include an equal distribution of male and female patients. Patients treated with lepirudin ranged from 4 months to 11 years of age, while those treated with argatroban varied from a neonate to a 15-year-old. Bivalirudin was used in 2- and 5-year-old children.

While all direct thrombin inhibitors and danaparoid have been used with success for treatment of HIT in children, none has FDA approval for this indication in this population. Anticoagulants used in these cases include the direct thrombin inhibitors, lepirudin, argatroban, bivalirudin, and the factor Xa inhibitor, danaparoid. The most commonly used anticoagulant was lepirudin, followed by danaparoid, argatroban, and bivalirudin. All agents, regardless of its metabolic pathway, displayed similar bleeding incidences, and none seemed to carry a greater risk. Since there were an unequal proportion of cases represented by each agent, it is not possible to conclude which agent is the safest in this population. Prospective studies providing evidence for the efficacy and safety of these agents are needed.

Lepirudin doses were lower or equal to recommended adult doses, while starting doses for argatroban were identical to adult dosing. However, a wide range of infusion rates with argatroban were reported. This may reflect the wide range of ages represented in these cases, which represents various degrees of hepatic maturity. For the cases that reported danaparoid doses, the infusion rates varied and were patient-specific.

Implications for Pharmacy Practice

Dosing recommendations for the direct thrombin inhibitors and danaparoid are often extrapolated from adult dosing. While dosing formulas and allometric scaling may be appropriate for children older than 8 years, whose body composition and organ function approximates to an adult, these approaches have limited merit in young children and neonates. The developmental changes that occur during childhood may alter the pharmacokinetics of the anticoagulants.¹²¹ The metabolism route, ease of monitoring, and relative risk of bleeding of each anticoagulant should be considered in choosing appropriate therapy. An understanding of the extent organ maturity may help to predict the pharmacokinetics of the agent in the child.

CONCLUSIONS

Heparin-induced thrombocytopenia remains a life-threatening condition in the pediatric popula-

tion, and proper understanding of its risks and management are essential. Tools such as assays and probability tests can aid in proper diagnosis. The limited data and lack of guidelines in the pediatric population makes pharmacotherapeutic decisions challenging. Following diagnosis of HIT, treatment with direct thrombin inhibitors and danaparoid have been described using case reports; however, use has not been evaluated in large studies of children with HIT. Further knowledge of developmental pharmacology and pharmacokinetics can guide pharmacotherapeutic decisions and individualize dosing in children in the future.

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ABBREVIATIONS aPTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; CRRT, continuous renal replacement therapy; DTI, direct thrombin inhibitor; DVT, deep vein thrombosis; ECC, extracorporeal circulation; ECMO, extracorporeal membrane oxygenation; ELISA, enzyme-linked immunosorbent assay; FcγRII, Fc receptor; FDA, Food and Drug Administration; HIT, Heparin-induced thrombocytopenia; INR, international normalized ratio; LMWH, low-molecular weight heparin; LVAD, left-ventricular assist device; PF4, Platelet factor 4; PCI, percutaneous coronary intervention; UFH, unfractionated heparin

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