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REVIEW ARTICLE

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Heparin-induced thrombocytopenia complicating children after the Fontan procedure: Single-center experience and review of the literature

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Abstract

Heparin-induced thrombocytopenia (HIT) is a life-threatening complication of heparin therapy. The risk for HIT correlates with the cumulative dosage of heparin exposure. In Fontan patients, recurrent systemic anticoagulation, traditionally with heparin, is used to alleviate the thrombotic complications that may occur postoperatively when the venous pressure rises and the systemic venous flow into the pulmonary arteries becomes sluggish, putting them at increased risk. As a pressure gradient-dependent circulation, elevation in systemic venous pressure, most often by venous thrombosis, contributes to circuit failure. Therefore, when HIT complicates patients after the Fontan procedure, it is associated with a high thrombotic morbidity and mortality; thus, a high index of suspicion is mandatory, based on the clinical signs of HIT. It is crucial to intervene early with alternative anticoagulants when HIT is suspected as this step may improve outcome in these patients.

KEYWORDS

anticoagulation, Fontan procedure, heparin-induced thrombocytopenia

1 | INTRODUCTION

The Fontan procedure was introduced in 1968 to treat the patients with tricuspid atresia.[1] Nearly, half a century and quite a few modifications later, this surgical approach has subsequently been applied to a range of complex univentricular congenital heart malformations in which a biventricular repair cannot be achieved. Such univentricular physiology is palliated by a three-stage intervention in which the systemic and pulmonary circulations are separated to normalize both the volume load on the ventricle and the level of blood oxygen.[2]

Although it has undergone numerous improvements and modifications over the years, thrombosis and thromboembolic events remain a major cause of morbidity and mortality after the Fontan procedure.[3] As a pressure gradient–dependent circulation, when venous thrombosis complicates the Fontan circulation, causing elevation in systemic venous pressure, it will eventually contribute to circuit failure. One of the possible mechanisms contributing to early postoperative venous thrombosis in Fontan patients is heparin-induced thrombocytopenia (HIT).

Heparin-induced thrombocytopenia is a prothrombotic, immune-mediated complication of unfractionated and low-molecular-weight heparin (LMWH) therapy. Heparin-induced thrombocytopenia is characterized by moderate thrombocytopenia 5–10 days after initial heparin exposure, the detection of platelet-activating anti-platelet factor 4 (PF4)/heparin antibodies, and an increased risk of venous and arterial thrombosis.[4]

The antibody–PF4/heparin 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.[5] The antibody also activates endothelial cells by binding to surface PF4/heparin complexes and as a result increases the expression of tissue factor and generation of thrombin.[6]

The diagnosis of HIT is complicated and based on both clinical suspicion and pathologic confirmation. Clinical suspicion of HIT typically occurs with declining platelet counts in the setting of active heparin use, painful, or pruritic inflammatory (erythematous) or necrotic skin lesions (cutaneous HIT), and suspected venous thrombus. Laboratory testing for suspected HIT includes immunologic assays, such as the PF4 enzyme-linked immunosorbent assay (ELISA) and particle gel immunoassay (PaGIA), which detect circulating anti-PF4/heparin antibodies. Although immunoassays are available in most medical centers,[7] they have a poor specificity (74%-86%) and anti-PF4/heparin antibodies can be detected in patients without HIT.[8] Functional assays, including the gold standard ^{14}C-serotonin release assay (SRA), measure platelet-activating effects of anti-PF4/heparin antibodies with >95% sensitivity and specificity for HIT.[9] The management of patients with suspected HIT includes immediate discontinuation of all sources of heparin and the initiation of an alternative anticoagulant.

Heparin-induced thrombocytopenia is infrequently recognized in pediatric patients,[10] especially neonates, and, when present, has been said not to carry major thrombotic morbidity and mortality.[11,12] The highest incidence of pediatric HIT has been found in pediatric intensive care units, especially those caring for patients after cardiac surgery.[13]

In this report, we describe 6 patients in our institution who underwent the Fontan procedure and were diagnosed with HIT.

2 | CASE REPORTS

Data of primary cardiac diagnosis, heparin required interventions, alternative anticoagulants, and outcome are summarized in Table 1. Patient 3 was similar to patient 1 in his clinical course without adding any additional necessary data.

2.1 | Patient 1

In February 2009, a 7-year and 3-month-old boy with double-inlet left ventricle pulmonary valve stenosis and hypoplastic right ventricle had a fenestrated extracardiac Fontan. He had previously undergone bidirectional Glenn with pulmonary artery division and mitral valvuloplasty. He had 4 associated heparin exposures.

After the surgery, he had massive bleeding (20 cc/kg/h) and after 2 hours was taken back to the operating room (OR) where he again was connected to cardiopulmonary bypass (CPB) with complete control of the bleeding. He was successfully extubated on postoperative day (POD) 1 and was weaned of vasoactive support on POD 2. Unfractionated heparin (UFH) continuous infusion (with activated partial thromboplastin time [aPTT], 50–70 s) was discontinued and LMWH was initiated simultaneously with warfarin (initial dose of 0.1 mg/kg with a target international normalized ratio [INR] of 2–3). His platelet count upon arriving from the OR was 240 $\times$ 10^9/L gradually decreasing to 80 $\times$ 10^9/L over the next 4 days. The patient was hemodynamically and respiratory stable, chest tubes were taken out on POD 4, liver enzymes were normalized, and no clinical or laboratory signs of infection were evident. On POD 7, platelet count decreased to 55 $\times$ 10^9/L; thus, HIT was suspected and supported by positive PaGIA test the next day. Low-molecular-weight heparin and warfarin were discontinued and bivalirudin was initiated by continuous infusion. Echocardiography was done the same day and flow acceleration was noticed within the Fontan canal without a clear evidence of thrombus. This finding resolved after 2 weeks in follow-up examination. Three days after bivalirudin initiation, platelet count rose to 120 $\times$ 10^9/L and 270 $\times$ 10^9/L a week later. After platelet count normalization, warfarin treatment was resumed, in addition to bivalirudin infusion, until achieving an INR of >2 6 days later on POD 24. Bivalirudin was discontinued and the patient was discharged from the hospital a week later, on POD31. He was seen in the cardiology clinic 1, 2, and 6 months after discharge and was doing well. After his last visit on September 2009, he was lost to follow-up.

2.2 | Patient 2

In March 2009, a 5-year and 4-month-old boy with pulmonary valve stenosis, D-transposition of the great arteries, hypoplastic right ventricle, and bilateral SVC, had a nonfenestrated extracardiac Fontan. He had previously undergone bilateral, bidirectional Glenn with pulmonary artery division. He had 3 associated heparin exposures.

At the end of the surgery, separation from CPB was difficult with the support of adrenaline (0.3 μg/kg/min), noradrenalin (0.3 μg/kg/min), and milrinone (0.75/μg/kg/min). His blood pressure was borderline and required repeated boluses of colloids and blood products. Vasopressin infusion of 0.0003 units/kg/min was initiated on POD1. He had massive serous drainage from his chest tubes (>100 cc/kg/day) during the first 3 PODs. The pulmonary artery pressure measured 19–23 mm Hg by a central venous catheter in the SVC. His blood oxygen saturations were in the low 90s and were attributed to pulmonary arteriovenous malformations. A few hours after his arrival from the OR, UFH infusion was initiated with target aPTT of 50–70 seconds. During the first 3 PODs, his platelet count ranged between 120 $\times$ 10^9/L and 170 $\times$ 10^9/L. On POD 3, after no signs of improvement were seen, he was taken to the OR and 5-mm fenestration was created between the Fontan canal and the right atrium with immediate hemodynamic improvement. He returned to the cardiac intensive care unit with the support of adrenaline (0.1 μg/kg/min), noradrenalin (0.15 μg/kg/min), which he was weaned from CPB on the same day, vasopressin (0.0003 units/kg/min), and milrinone (1 μg/kg/min). His blood oxygen saturations were 76%-82%. On POD 5, platelet count decreased to 50 $\times$ 10^9/L. White blood cell count increased to 24 $\times$ 10^9/L and C-reactive protein (CRP) was 120 mg/L and stable. Blood cultures were taken and antibiotic treatment was started. The patient remained hemodynamically stable with further decrease in inotropic support. Owing to high oxygen requirements and inhaled nitric oxide (iNO), he remained mechanically ventilated. On POD 7, his oxygen blood

TABLE 1 Summary of Fontan patients from our institution who developed HIT

Patient no.	Primary diagnosis	Interventions and heparin exposure	Manifestations	Age at diagnosis/ POD	HIT confirmation	Alternative treatment	Outcome
1	Double inlet left ventricle Pulmonary valve stenosis Hypoplastic right ventricle Bulboventricular septal defect	11/2002: Cardiac catheterization 11/2002: Unilateral bidirectional Glenn, pulmonary artery division 06/2003: Mitral valvuloplasty 02/2009: Cardiac catheterization 02/2009: Fenestrated Fontan, extracardiac	Thrombocytopenia	7y3m/8	PaGIA	Bivalirudin; warfarin	SHD; LTF
2	Pulmonary valve stenosis Transposition of the great arteries Hypoplastic right ventricle Bilateral SVC	02/2004: Cardiac catheterization 02/2004: Bilateral bidirectional Glenn, pulmonary artery division 12/2008: Cardiac catheterization 03/2009: Nonfenestrated Fontan, extracardiac 03/2009: Fenestration creation 03/2009: Cardiac catheterization 03/2009: Fontan takedown 03/2009: ECMO	Massive thrombosis; thrombocytopenia	5y4m/7	HIPA	Bivalirudin	Exitus
3	Unbalanced atrioventricular canal Mitral valve stenosis Aortic valve stenosis Coarctation of the aorta	11/2005: Damus-Kaye-Stansel, aortic coarctation repair, right ventricle to pulmonary artery conduit 03/2006: Cardiac catheterization 03/2006: Unilateral bidirectional Glenn 04/2009: Cardiac catheterization 08/2009: Nonfenestrated Fontan, extracardiac	Thrombocytopenia	3y9m/5	PaGIA	Bivalirudin; warfarin	SHD; LTF
4	Double outlet right ventricle Malposition of the great arteries Ventricular septal defect Pulmonary valve atresia Hypoplastic left ventricle	02/2010: Blalock-Taussig shunt 06/2011: Cardiac catheterization 06/2011: Unilateral bidirectional Glenn 10/2012: Cardiac catheterization 11/2012: Fenestrated Fontan, extracardiac	Thrombocytopenia	2y9m/9	PaGIA; HIPA	Bivalirudin	Exitus
5	Double outlet right ventricle Malposition of the great arteries Ventricular septal defect Interrupted IVC with azygous continuation to left SVC Bilateral SVC	07/2006: Pulmonary artery banding, atrial septectomy 08/2007: Cardiac catheterization 09/2007: Bilateral bidirectional Glenn, pulmonary artery division 08/2013: Cardiac catheterization 11/2013: Fenestrated Fontan, extracardiac 11/2013: Cardiac catheterization 11/2013: Extensive Fontan and pulmonary arteries embolectomy	Massive thrombosis; thrombocytopenia	8y3m/5	PaGIA; HIPA	Bivalirudin; warfarin	SHD; LTF
6	Double inlet left ventricle L-Transposition of the great arteries Hypoplastic right ventricle Bulboventricular septal defect Coarctation of the aorta	04/2013: Aortic arch reconstruction, pulmonary artery banding 02/2014: Cardiac catheterization 02/2014: Damus-Kaye-Stansel, unilateral bidirectional Glenn, pulmonary artery debanding 02/2016: Cardiac catheterization 02/2016: Nonfenestrated Fontan, extracardiac	Skin necrosis; thrombocytopenia	2y11m/15	PaGIA; HIPA	Fondoparinux; warfarin	SHD

Abbreviations: HIPA, heparin-induced platelet aggregation; IVC, inferior vena cava; LTF, lost to follow-up; PaGIA, particle gel immunoassay; POD, postoperative day; SHD, survived to hospital discharge; SVC, superior vena cava.

saturation decreased to 65%–70% on FiO2 1 and iNO of 40 ppm. Echocardiography demonstrated extensive thrombus in the Fontan canal with markedly decreased flow velocity. In the presence of continued UFH treatment, low platelet count and thrombosis of the Fontan canal, HIT was highly suspected; thus, all UFH solutions were immediately discontinued with alternative anticoagulation with bivalirudin. Heparin-induced thrombocytopenia was confirmed on the same day by a positive HIPA test. The patient underwent cardiac catheterization, and extensive thrombosis of the Fontan canal extending to the left pulmonary artery was diagnosed. During the following night, the patient deteriorated hemodynamically and was taken to the OR for urgent intervention. He underwent Fontan takedown and during the weaning attempt from CPB it was noticed that there was a near complete obstruction of his Glenn secondary to thrombosis. The patient was connected to extracorporeal membranous oxygenator (ECMO) support and transferred back to the unit. During the following hours, he had disseminated thrombi formation despite effective anticoagulation with bivalirudin, repeatedly clotting the ECMO circuit. The patient died after several hours owing to circuit failure secondary to uncontrolled thrombosis.

2.3 | Patient 4

In November 2012, a 2-year and 9-month-old girl with double-outlet right ventricle, malposition of the great arteries, pulmonary valve atresia, ventricular septal defect, and hypoplastic right ventricle, had a fenestrated extracardiac Fontan. She had previously undergone Blalock–Thomas–Taussig shunt and bidirectional Glenn. She had 4 associated heparin exposures.

The patient was easily weaned from CPB and was successfully extubated in the OR. She was transferred to the cardiac intensive care unit without hemodynamic support with 2 L/min of O_2 via nasal cannula. A few hours after her arrival from the OR, UFH infusion was initiated for target aPTT of 50–70 seconds. On POD 3, UFH was discontinued and LMWH was initiated simultaneously with warfarin (initial dose of 0.1 mg/kg with a target INR of 2–3). During the first 5 PODs platelet count ranged between 120 $\times$ 10^9/L and 160 $\times$ 10^9/L. On POD 6, the patient was febrile (39.5°C). Blood tests showed leukocytosis of 24 $\times$ 10^9/L, CRP was 180 mg/L, platelet count dropped to 65 $\times$ 10^9/L. Blood and urine cultures were taken and antibiotic therapy was initiated. On the same day, she deteriorated and required reintubation and hemodynamic support with adrenaline of 0.2 μg/kg/min and noradrenalin of 0.2 μg/kg/min. On POD, 8 her platelet count dropped to 30 $\times$ 10^9/L and CRP increased to 230 mg/L. The option of HIT was raised and supported by a positive PaGIA test on the following day. All UFH solutions were immediately discontinued with alternative anticoagulation with bivalirudin. On POD 9, blood cultures returned positive for multidrug-resistant *Acinetobacter baumannii* and antibiotic therapy was changed to meropenem and colistin. Heparin-induced thrombocytopenia was confirmed by a positive HIPA test later that day. On POD 10, she had a sudden bradycardia followed by asystole, and despite the efforts of the team she died after an unsuccessful resuscitation. No postmortem examination was done as per the family's request.

2.4 | Patient 5

In November 2013, an 8-year and 3-month-old boy with double-outlet right ventricle, malposition of the great arteries, ventricular septal defect, interrupted IVC with azygos continuation to the left SVC, and bilateral SVC, had a fenestrated extracardiac Fontan. He had previously undergone pulmonary artery banding with atrial septectomy, bilateral, bidirectional Glenn with pulmonary artery division. He had 4 associated heparin exposures.

The patient was easily weaned from CPB and was successfully extubated in the OR. He was transferred to the cardiac intensive care unit on noradrenalin (0.08 μg/kg/min) with 2 L/min of O_2 via nasal cannula. A few hours after his arrival from the OR, UFH infusion was initiated for target aPTT of 50–70 seconds. By POD 1, he was hemodynamically stable without noradrenalin and in room air. On POD 3, the right leg was noticed to be cool with poor perfusion and weak peripheral pulses. Ultrasound Doppler of the right femoral artery demonstrated a thrombus that extended superiorly toward the iliac artery; thus, UFH treatment was continued. We assumed that the thrombus was secondary to the right femoral arterial catheter that was taken out on POD 2. Platelet count during the first 4 days ranged between 65 $\times$ 10^9/L and 90 $\times$ 10^9/L. On POD 5, the platelet count decreased to 50 $\times$ 10^9/L; HIT was suspected and supported by positive PaGIA test the same day. All UFH solutions were immediately discontinued with alternative anticoagulation with bivalirudin. Heparin-induced thrombocytopenia was confirmed by a positive HIPA test the following day. On POD 6, there was a decrease in blood pressure that required inotropes and volume. Chest x-ray revealed bilateral significant pleural effusions. Echocardiography was done and a big thrombus extending from the Fontan canal to the right pulmonary artery was diagnosed. The patient underwent cardiac catheterization, which confirmed the diagnosis (Figure 1), and was taken immediately to the OR for extensive

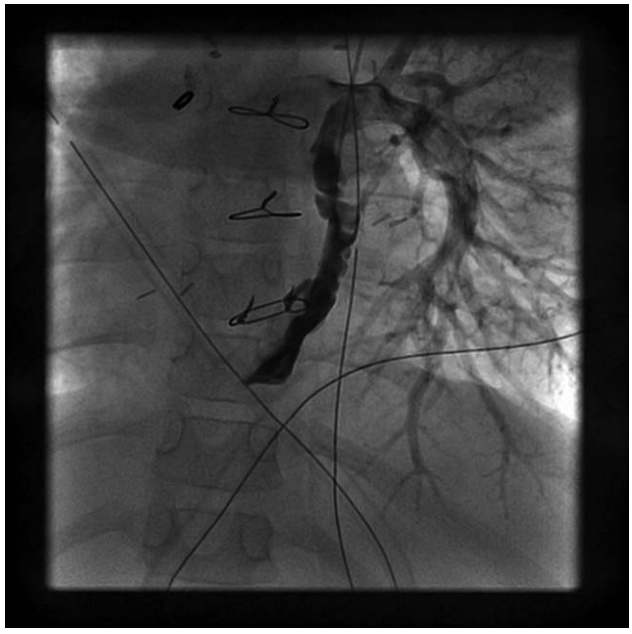

FIGURE 1 Thrombosis of the Fontan canal with complete occlusion of the right pulmonary artery in patient 5 from Table 1

Fontan and pulmonary arteries thrombectomy. Cardiopulmonary bypass was performed with bivalirudin as anticoagulant. He was transferred to the unit and mechanically ventilated without hemodynamic support. Bivalirudin was resumed shortly after the surgery. He was successfully extubated on POD 1 (POD 7 after the Fontan procedure) with 2 L/min of O_2 via nasal cannula. On POD 6, he was weaned from oxygen to room air. After 14 days of postoperative bivalirudin treatment and a platelet count of 250 $\times$ 10^9/L, warfarin was initiated, and after 6 days of concomitant therapy an INR of >2 was achieved on POD 26. Bivalirudin was discontinued and the patient was discharged from the hospital a week later, on POD 33. He was seen in the cardiology clinic for 2 years after the surgery and was doing well. After his last visit in December 2015, he was lost to follow-up.

2.5 | Patient 6

In February 2016, a 2-year and 11-month-old girl with double-inlet left ventricle, L-transposition of the great arteries, hypoplastic right ventricle, and coarctation of the aorta, had a nonfenestrated extracardiac Fontan. She had previously undergone aortic arch reconstruction with pulmonary artery banding, Damus–Kaye–Stansel procedure with bidirectional Glenn, and pulmonary artery debanding. She had 4 associated heparin exposures.

The patient was weaned from CPB and was successfully extubated in the OR. She was transferred to the cardiac intensive care unit on adrenaline (0.05 μg/kg/min) and noradrenalin (0.1 μg/kg/min) with 3 L/min of O_2 via nasal cannula. A few hours after her arrival from the OR, owing to gradual hemodynamic deterioration with increased lactate up to 110 mg/dL and massive drainage from the chest tubes, she was reintubated. Hemodynamic support was increased up to adrenaline (0.2 μg/kg/min), noradrenalin (0.2 μg/kg/min), and milrinone (0.75 μg/kg/min). Unfractionated heparin infusion was initiated for target aPTT of 50–70 seconds. She was stabilized with marked decrease in chest tubes drainage, and lactate decreased to 34 mg/dL during the following 2 days. She underwent a second extubation on POD 3. After the extubation, additional improvement was noticed with further decrease in hemodynamic support to adrenaline (0.05 μg/kg/min), noradrenalin (0.05 μg/kg/min), and milrinone (1 μg/kg/min). Lactate was 12 mg/dL and there was nearly no drainage from the chest tubes. By POD 6, she was weaned from hemodynamic support, stable in room air, with normal blood oxygen saturation. Concomitant treatment with warfarin was initiated for a target INR of 2–3. After 3 days of warfarin treatment, on POD 9, erythematous rash was noticed on the lower extremities. Laboratory results showed hemoglobin of 14 g/dL, platelet count of 160 $\times$ 10^9/L, aPTT of 62 seconds, and INR of 1.5. D-Dimer as well as renal function tests and liver enzymes were normal. Warfarin was discontinued. The consultation of dermatologist was ordered and performed on POD 13 with a suspicion of skin necrosis secondary to cutaneous HIT. In the absence of thrombocytopenia, PaGIA test was taken but UFH infusion was not discontinued. On POD 15, PaGIA test returned positive and all UFH solutions were immediately discontinued with alternative subcutaneous Fondaparinux treatment. Heparin-induced thrombocytopenia was confirmed by a positive HIPA test on the following day. The patient remained stable, with only a slight decrease in platelet count to 130 $\times$ 10^9/L. The cutaneous manifestations resolved within 5 days of UFH discontinuation. The patient was discharged from the hospital on POD 22 on daily Fondaparinux treatment. One month after discharge, concomitant treatment with warfarin was initiated until a target INR was reached and Fondaparinux was discontinued. The patient is doing well and last seen at the clinic in October 2017.

3 | DISCUSSION

The apparent high prevalence of HIT in patients with congenital heart disease exposed to CPB may be related to their repeated exposure to UFH in the setting of platelet activation. Such patients are exposed to UFH either to maintain catheter patency or because of anatomical indications, during cardiac catheterization or angiography, during CPB, and during the use, if required, of supportive ventricular assist devices, extracorporeal membrane oxygenation, and hemodialysis.[14]

Zhang et al.[15] found that the children who develop antibodies against the PF4/heparin complex had a significantly higher rate of postoperative thrombotic events than those who lacked these antibodies, and the risk of thrombosis increased with antibody titer. Antibodies to PF4/heparin were detected in 32.4% of their patients treated with UFH during Fontan completion. Cardiopulmonary bypass is known to induce strong platelet activation and the release of a large amount of PF4 into the plasma. This is one possible reason for the high frequency of the detection of PF4/heparin IgG after cardiac surgery. Bauer et al.[16] found that 50% of adult patients undergoing CPB had HIT antibodies postoperatively as detected by antigen assay. However, Selleng et al.[17] prospectively screened 581 cardiac surgery patients for heparin-dependent antibodies by PF4/heparin immunoassay and platelet activation test, and performed daily platelet counts (until day 10) with 30-day follow-up. They suggested that early-onset and persisting thrombocytopenia in postcardiac surgery patients are rarely owing to HIT, even when antibody tests are positive. One possible reason is that the typical onset of HIT coincides with the time period in which the platelet count typically falls to thrombocytopenic levels owing to perioperative hemodilution. In fact, recent guidelines suggest that clinicians should consider a fall in the platelet count to 50% of baseline between PODs 5 and 14 to represent potential HIT, and should order prompt laboratory investigations for HIT antibodies.[18] Exposure to heparin is associated with a substantial risk of developing antibodies to the heparin/PF4 complex (HIT antibodies). The appearance of HIT antibodies predicts lower postoperative thrombocytopenia and higher frequency of thrombotic events. When HIT antibodies are being detected after CPB, reexposure to heparin should be avoided and the patient should be managed at a high risk for thrombotic events.[15]

There are anecdotal reports of Fontan patients with HIT in the literature[19–21] (Table 2). Zhang et al.[15] have reported that HIT-related thrombosis was identified in a total of 11 of 105 patients (10.5%) on

TABLE 2 Summary of Fontan patients who were previously described in the literature

Patient no.	Primary diagnosis	Interventions and heparin exposure	Manifestations	Age at diagnosis/POD	HIT confirmation	Alternative treatment	Outcome
1. Hofer et al.[19]	Double outlet right ventricle Criss-cross heart Malposition of the great arteries Ventricular septal defect Hypoplastic right ventricle Pulmonary valve atresia	11/2009: Cardiac catheterization 11/2009: Norwood procedure with Sano shunt 02/2010: Cardiac catheterization 02/2010; Unilateral bidirectional Glenn 11/2010: Cardiac catheterization 11/2010: Fenestrated Fontan, lateral tunnel	Thrombocytopenia	3y/6	4Ts high risk; IgG-specific ELISA test; HIPA	Argatroban; phenprocoumon	N/A
2. Hofer et al. [19]	Hypoplastic left heart syndrome Mitral valve atresia Aortic valve atresia	07/2008: Norwood procedure with Sano shunt 11/2008: Sano shunt replacement 11/2008: Extracorporeal membranous oxygenator, RSV infection 03/2009: Cardiac catheterization 03/2009: Unilateral bidirectional Glenn 10/2012: Cardiac catheterization 10/2012: Fenestrated Fontan, lateral tunnel	Thrombocytopenia; Fontan tunnel thrombosis	4y/7	4Ts high risk; IgG-specific ELISA test; HIPA	Argatroban; phenprocoumon	N/A
3. Porcelli et al. [20]	Double inlet left ventricle Aortic valve stenosis Hypoplastic aortic arch	Norwood procedure Cardiac catheterization Bidirectional Glenn Cardiac catheterization 11/1998: Fontan operation	Thrombocytopenia; inferior vena cava thrombosis	2y/17	HIPA	None	Exitus
4. Porcelli et al. [20]	Tricuspid valve atresia Pulmonary valve atresia Hypoplastic right ventricle	Blalock-Taussig shunt Cardiac catheterization Bidirectional Glenn Cardiac catheterization 09/1999: Fontan operation	Thrombocytopenia; left femoral artery thrombosis	3y/6	IgG-specific ELISA test; HIPA (negative SRA)	None	SHD
5. Knoderer et al. [21]	Hypoplastic left heart syndrome	Norwood procedure Cardiac catheterization Hemi-Fontan Cardiac catheterization Fenestrated Fontan operation, lateral tunnel Extracorporeal membranous oxygenator	Thrombocytopenia; Fontan tunnel thrombosis; right common femoral and external iliac veins thrombosis	1y9m/8	IgG-specific ELISA test	Lepirudin	SHD

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HIPA, heparin-induced platelet aggregation; PaGIA, particle gel immunoassay; POD, postoperative day; SHD, survived to hospital discharge; SRA, serotonin release assay.

TABLE 3 Characteristics of alternative anticoagulants

Agent	Class	Dose	Monitor	Clearance	t1/2	Antagonist	Comments
Lepirudin Refludan®	Irreversible direct thrombin inhibitor	0.4 mg/kg IV Bolus (max 44 mg) 0.15 mg/kg/h (max 16.5 mg/h)	aPTT ratio target 1.5-2.5	Renal	80–90 min (depends on renal function)	None	According to the US FDA, Baxter Healthcare Corporation made the decision to discontinue Refludan® for injection on May 31, 2012
Argatroban	Reversible direct thrombin inhibitor	No bolus indicated 2 μg/kg/min (max 10 μg/kg/min)	aPTT ratio target 1.5-3	Hepatic	30–50 min (depends on hepatic function)	None	Reduced the relative risk of death, new thrombosis, or other complications in patients with HIT in clinical trials[a] Before administration discontinue heparin and obtain baseline aPTT[a] Interferes with fibrin generation, platelet aggregation, and factor XII activation[a] Increases in a dose-dependent manner, aPTT, the ACT, the PT, the INR, and the thrombin time[a]
Bivalirudin Angiomax®	Reversible direct thrombin inhibitor	0.75 mg/kg IV Bolus 0.2 mg/kg/h	aPTT ratio target 1.5–2.5	Renal (20%) proteolysis (plasma) (80%)	25–30 min	None	IV/SC[a] Interferes with fibrin generation, platelet aggregation, and factor XII activation[a]
Danaparoid Orgaran®	Heparinoid, selective inhibitor of anti-factor *Xa*	30 units/kg IV Bolus 1.2-2 units/kg/h	Anti-*Xa* activity target 0.4–0.8 IU/mL	Renal	18–24 h	Protamine does not reverse the bleeding effects	Organon, Inc., discontinued manufacturing Orgaran® on August 14, 2002 owing to a shortage in drug substance
Fondaparinux	Indirect factor *Xa* inhibitor	5 mg (<50 kg), 7.5 mg (50–100 kg), 10 mg (>100 kg) SC qd	Anti-*Xa* activity can be monitored but laboratory monitoring is not necessary	Renal	18 h	Aripazine	Selectively inhibits factor *Xa* via antithrombin-dependent actions[a] Does not inhibit thrombin (factor IIa)[a] Depends on antithrombin III for activity[a]

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; IV, intravenous; PO, Per Os; PT, prothrombin time; SC, subcutaneous.
[a]Data are obtained from Truven Health Analytics Inc. Micromedex® solutions; www.micromedexsolutions.com.

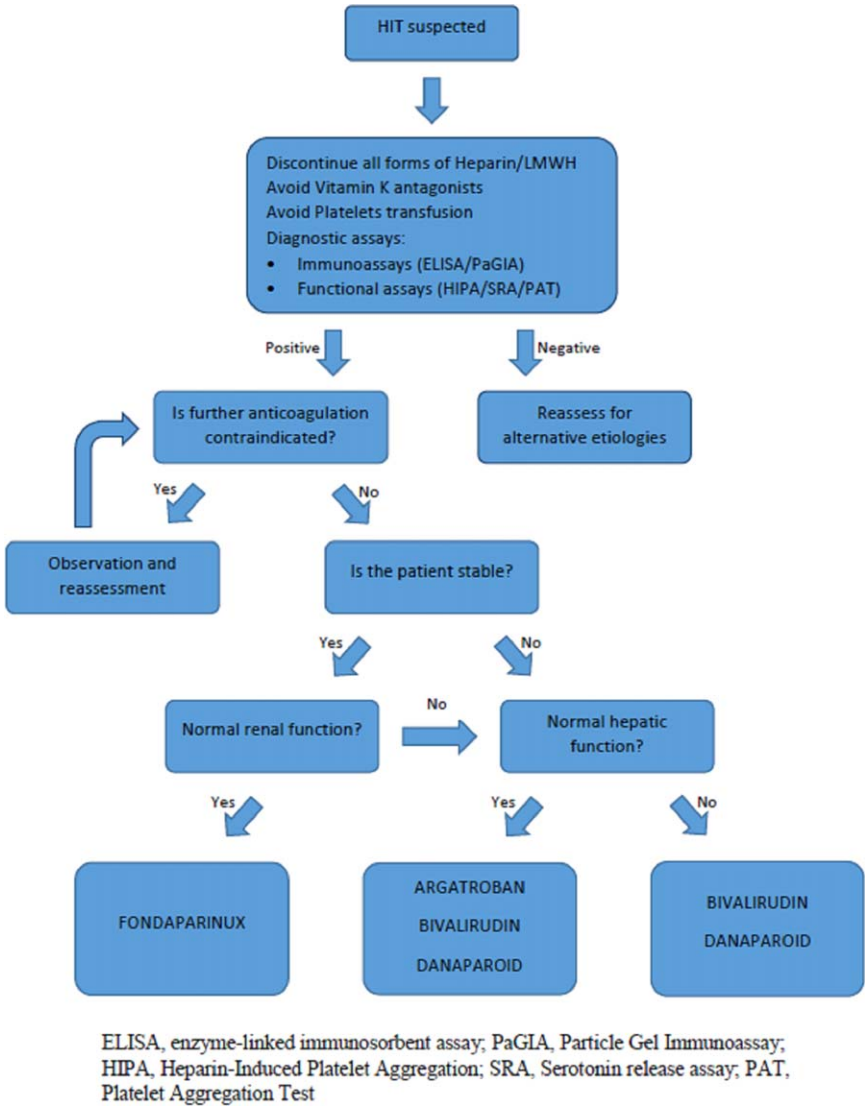

FIGURE 2 Diagnosis and treatment algorithm for suspected HIT

POD 6 after Fontan completion. The incidence of antiheparin/PF4 antibody seroconversion in older pediatric cardiac surgical patients is approximately 50% at 10 days postsurgery, similar to that reported in adult cardiac surgical patients.[22] Both age and previous exposure to UFH are correlated with the rate of seroconversion in adult patients. In contrast, the rate of seroconversion in the neonatal population was substantially lower. The age at Fontan completion is around 24 months with some variations according to different programs' policies, and way out of the neonatal period when the antiheparin/PF4 antibodies' seroconversion is low. Fontan completion is usually the third surgical intervention and occurs after repeated exposures to UFH (surgical interventions, cardiac catheterizations, etc), resulting in larger cumulative UFH dosage that significantly increases the rate of seroconversion.[13] The hemodynamics of the Fontan circulation may contribute to HIT via elevated venous pressure and sluggish flow in the cavopulmonary connections. It results in a procoagulant state, with abnormal levels of multiple clotting factors, including protein C, protein S, and antithrombin III, as well as increased platelet reactivity.[23,24] This state is aggravated by atrial arrhythmias and the possible presence of prosthetic material. This predisposition may explain the relatively high incidence of HIT found in our Fontan patients as well as in Zhang et al.'s study.[15]

The management of HIT includes the immediate discontinuation of all forms of heparin exposure, including lines flush solutions, and the administration of an alternative anticoagulant (such as direct thrombin inhibitors or factor *Xa* inhibitors)[25] (Table 3) even without the indication of the underlying condition. If another anticoagulant is not administered, then there is a substantially increased risk of symptomatic or fatal thrombus formation. Twenty to fifty percent of patients will progress to a clinically significant thrombotic event without further anticoagulation therapy, with a 30-fold increased risk of thrombosis than the normal populations.[26,27] Because of their HIT-promoting properties, treatments with LMWH, vitamin K antagonists during the acute phase of HIT, platelets transfusions, and implantable vena cava filters should be avoided.[28] Our proposed HIT management algorithm is shown in Figure 2.

4 | SUMMARY

Heparin-induced thrombocytopenia is a serious, antibody-mediated complication of heparin therapy. It confers significant risks of thrombosis and devastating, life-threatening, outcomes. Although HIT is a recognizable and treatable complication, because of its relative infrequency, patients are at increased risk for delayed diagnosis and significant morbidity. It is apparent that HIT is an intensely prothrombotic disorder and in the setting of patients after the Fontan procedure it is associated with a high thrombotic morbidity and mortality; thus, a high index of suspicion is mandatory, based on the clinical signs of HIT. It is crucial to intervene early with alternative anticoagulants when HIT is suspected as this step may improve outcome in these patients. Fontan completion at least 3 months after previous exposure to UFH, as in preoperative cardiac catheterization, is an option to consider as it minimizes the risk for early HIT. Further clinical research into the relationship between the PF4/heparin antibody level and the risk for HIT development in this population can be beneficial in the aspect of preoperative risk assessment. Finally, advancement in alternative anticoagulants in the pediatric population is critical so that therapy can be optimized without placing these patients at undue risk.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

All authors read and approved the final version of the manuscript.
Carried out initial literature search and review: Pollak
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Manuscript review and revision: Pollak, Mishaly, Kenet, Vardi
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