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PEDIATRIC MECHANICAL CIRCULATORY SUPPORT: PATHOPHYSIOLOGY OF PEDIATRIC HEMOSTASIS AND POSTOPERATIVE MANAGEMENT ALGORITHMS

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Chronic heart failure (CHF) against the background of congenital heart disease, mostly in early childhood, or various forms of cardiomyopathies, more common in teenage age, represents an important cause of morbidity and mortality in the pediatric population [1, 2]. Due to the increase in the number of patients suffering from refractory end-stage CHF over the last two decades, and the current shortage of donor organs in pediatric practice, the issue of long-term mechanical circulatory support (MCS) is becoming increasingly a pressing problem. Patient management is a multidisciplinary task, since prolonged use of anticoagulant and antiplatelet therapy to prevent ventricular thrombosis has potentially life-threatening complications – acute hemorrhagic stroke and bleeding of varying severity.

Keywords: heart failure in children, long-term mechanical circulatory support, anticoagulant therapy, antiplatelet therapy.

GENERAL CHARACTERISTICS OF EXISTING SYSTEMS OF LONG-TERM MECHANICAL CIRCULATORY SUPPORT

Mechanical circulatory support (MCS) is a general term that currently describes various types of mechanical devices capable of fully or partially replacing the patient's heart function [3]. Specific definitions for different types of MCSs are applied depending on their purpose, duration of application, cannulation options and blood flow type. Long-term MCS systems include ventricular assist devices, which can replace the function of the left and/or right ventricles of the patient's own heart. The main characteristics of the currently available long-term MCS systems used in pediatric practice are presented in Table 1.

The first publications on successful implantation of continuous-flow long-term MCS systems in teenagers with end-stage CHF appeared in the early 2010s [4, 5]. In the initial stages of the program, these systems were implanted in children weighing 50 kg or more, taller than 150 cm, and with a body surface area (BSA) >1.5 m^2. Subsequently, the anthropometric criteria for implantation of such systems were expanded. For instance, according to the Fourth Annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs), published in 2020, 1,031 MCS devices were implanted in patients under 19 years of age between September 19, 2012, and December 31, 2019. Intracorporeal continuous-flow long-term MCS devices were implanted in children aged 13.2 ± 3.9 years (n = 365). The number of paracorporeal continuous pumps implanted was 212, the average age of the patients was 3.6 years. In a group of children aged 2.7 years, pulsatile paracorporeal pumps were used most frequently (n = 230). It was shown that the incidence of cerebrovascular and hemorrhagic complications depends on the type of implanted device [6].

COMPLICATIONS ASSOCIATED WITH HEMOSTATIC DYSFUNCTION

Compared to the adult population, the pediatric cohort requiring the use of MCS devices is characterized by increased incidence of hemorrhagic and thrombotic complications, which is explained by changes in the hemostatic system, taking into account the age of the child, the specific course of some congenital heart defects, and the effect of components of the assisted circulation system on the coagulating blood system. Direct contact of the patient's blood with biomaterials of the system leads to activation of the complement system and production of inflammatory cytokines [7]. Normally, endothelial cells produce anticoagulant and procoagulant factors, and contribute to maintaining normal homeostasis in the body. Blood contact with non-endothelialized biomaterials activates a protective response, the degree of which may vary depending on the patient's individual characteristics. As a result, there is an imbalance of physiological coagulation due to increased consumption of

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anticoagulation factors and stimulation of procoagulant production [8, 9].

It should be noted that in the group of newborns and children in their first year of life requiring the use of MCS, the issue of anticoagulant therapy dosage selection is particularly relevant. This is primarily due to "developmental haemostasis" – physiological changes in the blood coagulation system, which depend on the child's age [10]. A specific feature of newborns is physiologically low level of vitamin K-dependent coagulation factors, such as factors XI and XII, prekallikrein, high-molecular-weight kininogen, whose level gradually increases and reaches the level of an adult by six months of life. Von Willebrand factor (vWF) and factor VIII levels have been shown to be elevated at birth and in the first 3 months of life [11, 12].

In addition to physiological age-related features in the hemostasis system, it is necessary to remember about acquired coagulation defects. For instance, young children with cyanotic congenital heart disease often have hypercoagulation syndrome on the background of polycythemia and increased levels of platelets, fibrinogen and coagulation factors V and VIII. In older people, such a condition leads to systemic circulation stasis against the background of CHF, which is accompanied by liver dysfunction with thrombocytopenia, decreased production of clotting factors and increased fibrinolytic activity [13].

The latest generation of long-term MCS devices contain biomaterials that allow maximum bio- and hemocompatibility when in contact with the human body. However, no surface of the systems used today has complete identity with the human endothelium.

A history of gastrointestinal angiodysplasia and congenital coagulopathy can alter the pharmacokinetics of antiplatelet and anticoagulant therapy in patients on long-term MCS.

Development of hemolysis against the background of direct exposure of erythrocytes to a mechanical heart pump, characterized by the presence of serum free hemoglobin >40 mg/dL and increased lactate dehydrogenase (LDH) levels, leads to production of vWF that plays an important role in impaired hemostasis against the background of ventricular heart operation [14, 15].

It has been shown that roller pumps, as well as short- and long-acting axial flow devices cause higher levels of hemolysis in comparison with centrifugal blood pumps. For example, according to the literature, higher baseline hemolysis levels were seen in patients after HeartMate II implantation compared with Heartware and HeartMate III [16]. Despite these findings, the choice of an implantable long-term MCS system, in pediatric practice, primarily depends on the child's anthropometric data [17].

ANTICOAGULANT THERAPY

To date, there are no unified guidelines for administration of anticoagulant and antiplatelet therapy in pediatric patients who are implanted with long-term MCS pumps. Standard management regimens for this category of patients include the use of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) in the early postoperative period, followed by transition to warfarin in combination with antiplatelet agents (aspirin or clopidogrel).

HEPARIN USE IN THE EARLY POSTOPERATIVE PERIOD

The use of heparin in the early postoperative period is associated with the risk of complications of varying severity, especially in newborns and children in their first year of life, and, accordingly, a number of problems for the clinician.

1. Heparin dose variability makes it difficult to maintain a standard therapeutic dose of the drug [18].
2. Incidence of heparin-induced thrombocytopenia is about 1%, which is associated with an adverse prognosis for life [19, 20, 21].
3. Heparin is a biological compound, so allergic reactions of varying severity, up to and including anaphylactic shock with mortality, are possible [22].

Table 1

Long-term MCS systems in pediatric practice

Name	Pumping mechanism	Flow type	Maximum flow	Support type	Used in children
Syncardia TAH	Pneumatic	Pulsatile	7–9 L/min	Biventricular	Teenagers
Berlin Heart EXCOR®	Pneumatic	Pulsatile	3–7.2 L/min	LVAD, RVAD, Biventricular	>3 kg
Jarvik 2000 Jarvik 2015	Axial	Continuous	7 L/min 3 L/min	LVAD	Teenagers >30 kg >8 kg
HeartMate II	Axial	Continuous	3–10 L/min	LVAD	Teenagers
HeartMate III	Centrifugal	Continuous	10 L/min	LVAD, RVAD, Biventricular	Teenagers
HeartWare	Centrifugal	Continuous	10 L/min	LVAD	>15 kg

Note: LVAD, left ventricular assist device; RVAD, right ventricular assist device.

4. Prolonged use of heparin can lead to osteoporosis and spontaneous bone fracture due to inhibition of osteoblast formation [23].

To date, various monitoring tests have been proposed to evaluate the effectiveness of heparin therapy. The most common are presented in Table 2.

Ongoing heparin therapy in most cases is monitored by determining the aPTT.

It is known that a sufficient level of endogenous antithrombin III (AT III) is necessary for effective heparin therapy. However, in newborns, serum AT III levels are physiologically low, which may lead to ineffective heparinization and require administration of fresh frozen plasma or recombinant antithrombin drugs [24].

Bivalirudin, a direct thrombin inhibitor, inhibits all reactions catalyzed and induced by thrombin, including thrombin formation, activation of clotting factors V, VIII and XIII, activation of protein C and platelet aggregation. The effect of the drug is not related to the amount of circulating endogenous AT III in blood plasma, which allows for a more stable anticoagulant effect in this patient cohort [25].

Bivalirudin can be used:

– As an alternative to heparin in anticoagulant therapy, especially in heparin-induced thrombocytopenia (HIT);
– When it is impossible to achieve and maintain therapeutic aPTT values on the background of heparin infusion;
– In patients with signs of developing thrombosis despite heparin therapy [26].

When prescribing bivalirudin in the early postoperative period, the dose is selected depending on the risks of postoperative bleeding. At high risks of bleeding, it is recommended to maintain the target aPTT value at 50–60 s; at planned course of the postoperative period, the drug dose is titrated until the aPTT level reaches 60 to 80 s; at high risks of prosthetic heart valve thrombosis, maintaining the target aPTT value at 70 to 90 s is recommended [27].

To date, there have been few reports in the literature on administration of bivalirudin in patients after ventricular assist device implantation.

Today, there are three main protocols for anticoagulation therapy used in pediatric patients on long-term MCS (Table 3).

As can be seen from Table 3, each of the three protocols has its own differences, but they are all based on therapy that includes a combination of antiplatelet and anticoagulant drugs.

The Edmonton protocol was the first detailed guideline for anticoagulant and antiplatelet therapy in children after implantation of paracortical systems for long-term MCS and included administration of UFH, LMWH, warfarin, aspirin or clopidogrel. Heparin dose was adjusted according to the anti-Xa level and under control of aPTT, the target values of which were 1.5–2.5 times higher than the baseline values. Initiation of antiplatelet therapy was determined by thromboelastogram values [31].

In 2016, a prospective study by Steiner and coauthors analyzed the effectiveness of anticoagulant and antiplatelet therapy, the incidence of severe complications and the

Table 2

Tests for determining the effectiveness of heparin therapy

Test name	Method	Advantages	Disadvantages
Activated clotting time (ACT)	Whole blood clotting time is measured in seconds using activators (kaolin or celite)	Widely used in clinical practice Results are received within seconds Possibility of bedside testing	In some cases, ACT does not accurately reflect the effect of heparin due to an increase in the indicator regardless of the dose of the drug against the background of: – Hemodilution – Thrombocytopenia – Hypothermia – Hypofibrinogenemia – Lack Of Clotting Factors
Activated partial thromboplastin time (aPTT)	Internal and external pathways of the coagulation cascade are evaluated. It is carried out by adding an activator and phospholipid to the patient's plasma, followed by addition of calcium and measuring the clotting time in seconds	Widely used in clinical practice Rapid results	Decreased accuracy of results in vitamin K and/or factor VIII deficiency
Anti-factor Xa assay	A reagent and chromophore substrate are used to quantify the heparin-AT complex	Rapid results	Inaccurate assessment of the effectiveness of heparin in: – Hyperbilirubinemia – Hemolysis – Hyperlipidemia – High Antithrombin Levels

need for ventricular assist device replacement in children on paracortical long-term MCS who received therapy according to the Edmonton Protocol. Bleeding incidence was 43% of cases, of which in 24% of the cases, this complication was associated with the administered blood thinning therapy and was observed mainly during the first 14 days after surgical intervention. From day 4 to day 30 after implantation, 28% of patients were diagnosed with acute impairment of cerebral circulation and 9% of them were associated with ongoing drug therapy. The mechanical device had to be replaced in 56% of cases because of thrombotic complications. So, the authors concluded that new approaches for antiplatelet and anticoagulant therapy in children on long-term MCS are needed [32].

Ed Peng et al. analyzed the outcomes of implantations of Durable Continuous-Flow Mechanical Circulatory Support (HVAD; HeartWare, Framingham, MA) devices in 12 children between 2010 and 2015. The median age of the children was 7.1 years (3.7 to 17.0 years); four patients were aged 5 years or less. Indications for LVAD implantation in 11 cases were chronic heart failure that developed against a background of dilated cardiomyopathy, in one case the system was implanted due to cardiac graft dysfunction against the background of acute rejection. The mean length of support was 150 days (range, 16 to 638). Anticoagulant therapy was started 24 hours after implantation, provided the rate of drainage discharge was <1 ml/kg/hour for three consecutive hours. Revision of the mediastinum to stop bleeding was required in two patients. In two cases, device thrombosis was diagnosed without development of neurological complications. The 1-year actuarial survival was 100% with no neurologic events [33].

David N. Rosenthal et al. compared the effect of the Edmonton and Stanford protocols of anti-thrombotic therapy in children for extracorporeal long-term MCS on the incidence of acute cerebrovascular accidents. The Edmonton antithrombotic guideline cohort included children implanted before September 2012 when dual antiplatelet therapy was used with doses titrated to thromboelastography and/or platelet mapping. The second cohort of the Stanford Modified Antithrombotic Guideline cohort, which included children implanted on or after September 2012 when triple antiplatelet therapy was used routinely and where doses were uptitrated to high, weight-based dosing targets. So, target doses of aspirin, clopidogrel and dipyridamole were higher, with less dosing variability in the Stanford cohort than in the Edmonton cohort ($p < 0.003$). The incidence rate of stroke in the Stanford cohort was 84% lower than in the EG cohort (0.8 vs 4.9 events per 1,000 days of support, $p = 0.031$), and 86% lower than in the previous Investigational Device Exemption trial ($p = 0.006$) [34].

To date, the latest generation of the HeartMate III (Abbott Corporation) continuous-flow intracorporeal pump has been actively implanted in children with end-stage CHF. Matthew J. O'Connor et al. in their paper analyzed the results of HeartMate III implantations in 35 patients aged 8.8 to 47.3 years (median age of 15.7 years) and a median BSA of 1.74 (0.78 to 2.36) m^2 performed between December 2017 and September 2019 at 9 ACTION (Advanced Cardiac Therapies Improving Outcomes Network) centers. Dilated cardiomyopathy, dilated cardiomyopathy in neuromuscular disease (20%), and congenital heart disease (17%) were indications for implantation of ventricular assist devices in 63%.

The anticoagulant and antiplatelet therapy protocols had some differences due to the experience of the HeartMate III implantation center (Table 4).

As can be seen from Table 3, warfarin therapy in combination with aspirin was preferred and was used in almost the entire patient cohort. The authors showed that during the follow-up period (median follow-up 78 days) no complications such as acute cerebral circulation disorder, ventricular thrombosis and significant bleeding were reported [35].

Although the current standard anticoagulant therapy is most commonly given with vitamin K antagonist warfarin, this poses certain challenges associated with the need for frequent monitoring of the international normalized ratio, dietary compliance and repeated hos-

Table 3

Anticoagulant therapy protocols for long-term pediatric MCS

Protocol name	Early p/o period	Long-term p/o period	Antiplatelet agents	Monitoring	Other
Edmonton Protocol [28]	Heparin	Enoxaparin ≤12 months Warfarin >12 months	Dual antiplatelet therapy: Dipyridamole 4 mg/kg/day Aspirin 1 mg/kg/day	Thromboelastogram + platelet aggregation	
Stanford Protocol [29]	Heparin	Enoxaparin ≤12 months Warfarin >12 months	Triple antiplatelet therapy: Aspirin 30 mg/kg/day Dipyridamole 15 mg/kg/day Клопидогрел 1 mg/kg/day	None	Steroids in systemic inflammatory response
ACTION protocol [30]	Bivalirudin	Coumarin	Aspirin	Thromboelastogram + platelet aggregation	Steroids in systemic inflammatory response

Table 4

Combinations of anticoagulant and antiplatelet therapy for long-term MCS

Drug	n (%)
Unfractionated heparin	28 (77.8%)
Low-molecular-weight heparin	4 (1.1%)
Bivalirudin	8 (22.2%)
Warfarin	31 (86.1%)
Aspirin	34 (94.4%)
Clopidogrel	0
Dipyridamole	0

pitalizations associated with complications from sub- or over-therapeutic international normalized ratio values.

New direct-acting oral anticoagulants (direct thrombin inhibitors (dabigatran) or direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban and betrixaban) do not require laboratory monitoring. Potential disadvantages of these groups of drugs are their higher cost and shorter half-life compared with warfarin. This is associated with higher risk of thrombosis if the drug is missed. Currently, new direct-acting oral anticoagulants have begun to be considered as an alternative to vitamin K antagonists in the management of patients on long-term MCS systems.

The only randomized trial comparing the efficacy of phenprocoumon with dabigatran in patients after HeartWare ventricular implantation (HVAD) was terminated prematurely due to frequent thromboembolic complications in the group of patients taking dabigatran: 3 of 8 patients had ventricular thrombosis, one patient had transient ischemic attack [36].

The experience of using factor Xa inhibitors in this patient cohort is limited to single publications. For example, Parikh V. et al. reported seven patients who received anticoagulant therapy with rivaroxaban and apixaban in the postoperative period (one Heartmate II patient took rivaroxaban 15 mg daily, two HeartWare patients took rivaroxaban 15 mg daily, and four HeartWare patients took apixaban 5 mg twice daily). No thromboembolic complications were registered during the follow-up period of 1459 days, in 2 cases gastrointestinal bleeding developed in the late postoperative period (0.07 cases per patient per year) [37].

Schulte-Eistrup S. et al. reported on 22 patients after HeartWare implantation whose therapy was converted from vitamin K antagonists to apixoban at a dose of 5 mg daily in combination with aspirin (n = 10) or clopidogrel (n = 12) due to inability to regularly monitor the ongoing anticoagulant therapy. There were no fatal complications related to apixoban administration during the follow-up period of 408 ± 296 days (45–1554) [38].

In a retrospective randomized clinical trial, Song L et al. compared the incidence of stroke, bleeding, thrombotic complications, and death in patients after HeartMate III implantation by dividing them into two groups. The first group included 20 patients treated with warfarin; the second group (n = 15) received apixaban as anticoagulant therapy. During the 6-month follow-up period, there were no significant differences in complications and deaths between the two groups [39].

CONCLUSION

Peculiarities of postoperative management of children and adolescents after implantation of long-term MCS devices are crucial for stable operation of the ventricular assist device. Conscious anticoagulant and antiaggregant therapy, monitoring in the early and late postoperative period of the administered drug therapy, as well as control of laboratory parameters during conversion from one drug to another, can reduce the risks of bleeding and thromboembolic complications in this patient cohort.

Until recently, heparin and warfarin were used as the drugs of choice for anticoagulant therapy in patients on long-term mechanical circulatory support. With the emergence of new groups of anticoagulant drugs, interest in their use has increased significantly, which is associated with more convenient dose titration, absence of the need for regular monitoring of hemostasis parameters and low risks of postoperative complications against the background of ongoing treatment.

Muhammad Bakr Ghbeis et al. reported on their own experience of anticoagulant and antiplatelet therapy in the postoperative period in children requiring implantation of long-term MCS systems.

Examination before MCS implantation

1. ***Laboratory monitoring***
   a. *Mandatory examination:*
      – Determination of platelet count, prothrombin time, INR, aPTT, fibrinogen level, basic metabolic indicators
   b. *Additional examinations*
      – Thromboelastography with platelet mapping, C-reactive protein level, LDH, cystatin C, heparin-induced thrombocytopenia screening
2. ***Medical history and family history***
   – Bleeding and thrombosis history
      a. *With a burdened history, additionally:*
         – Anticardiolipin, beta-2 glycoprotein, lupus anticoagulant, factor V Leiden, prothrombin 20210A gene mutation, antithrombin 3 and protein S and C.

After MCS implantation:

1. ***Day zero after surgery***
   – After completion of hemostasis, bivalirudin administration at a dose of 0.1–0.3 mg/kg/h at an initial target aPTT of 50–60 seconds, with subsequent dose increases over several days until aPTT of 70 to 90 seconds is achieved.

2. ***First postoperative days***
- *Paracorporeal mechanical circulatory support*
  - Continuation of bivalirudin therapy. Start of antiplatelet agents within 1–2 weeks after implantation. If signs of fibrin formation or clot formation develop on the ventricular assist device, earlier initiation of antiplatelet therapy is possible.
- *Intracorporeal mechanical circulatory support*
  - Therapy with bivalirudin or unfractionated heparin in early stages with subsequent transition to indirect anticoagulants with maintenance of target INR of 2 to 3.5. On day 5 to day 7, antiplatelet agents should be added to the therapy.

The authors have shown effective use of this protocol in the management of children and adolescents after implantation of long-term MCS systems [40].

Changes in anticoagulant therapy strategy with the advent of the direct thrombin inhibitor bivalirudin, new oral direct-acting anticoagulants and direct Factor Xa inhibitors open up new perspectives in personalizing the approach in treating children implanted with long-term MCS systems.

The authors declare no conflict of interest.

REFERENCES

1. *Masarone D, Valente F, Rubino M, Vastarella R, Gravino R, Rea A et al.* Pediatric Heart Failure: A Practical Guide to Diagnosis and Management. *Pediatr Neonatol*. 2017; 58 (2): 303–312.
2. *Rossano JW, Shaddy RE.* Heart failure in children: etiology and treatment. *J Pediatr*. 2014; 165 (2): 228–233.
3. *Kreuziger LB, Massicotte MP.* Adult and pediatric mechanical circulation: a guide for the hematologist. *Hematol Am Soc Hematol Educ Program*. 2018; 30: 507–515.
4. *Owens WR, Bryant R 3rd, Dreyer WJ, Price JF, Morales DL.* Initial Clinical Experience With the HeartMate II Ventricular Assist System in a Pediatric Institution. *Artif Organs*. 2010; 34: 600–603.
5. *D'Alessandro D, Forest SJ, Lamour J, Hsu D, Weinstein S, Goldstein D.* First reported use of the Heartware HVAD in the US as bridge to transplant in an adolescent. *Pediatr Transplantation*. 2012; 16: 356–359.
6. *Morales DLS, Adachi I, Peng DM, Sinha P, Lorts A, Fields K et al.* Fourth Annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) Report. *Ann Thorac Surg*. 2020; 110 (6): 1819–1831.
7. *Ekdahl KN, Teramura Y, Hamad OA, Asif S, Duehrkop C, Fromell K et al.* Dangerous liaisons: complement, coagulation, and kallikrein/kinin cross-talk act as a linchpin in the events leading to thromboinflammation. *Immunol Rev*. 2016; 274 (1): 245–269.
8. *Himmelreich G, Ullmann H, Riess H, Rosch R, Loebe M, Schiessler A, Hetzer R.* Pathophysiologic role of contact activation in bleeding followed by thromboembolic complications after implantation of a ventricular assist device. *ASAIO J*. 1995; 41 (3): M790–M794.
9. *Jaffer IH, Fredenburgh JC, Hirsh J, Weitz JI.* Medical device-induced thrombosis: what causes it and how can we prevent it? *J Thromb Haemost*. 2015; 13 (suppl 1): S72–S81.
10. *Monagle P, Barnes C, Ignjatovic V, Furmedge J, Newall F, Chan A et al.* Developmental haemostasis. Impact for clinical haemostasis laboratories. *Thromb Haemost*. 2006; 95: 362–372.
11. *Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Powers P.* Development of the human coagulation system in the full-term infant. *Blood*. 1987; 70: 165–172.
12. *Andrew M, Paes B, Johnston M.* Development of the hemostatic system in the neonate and young infant. *Am J Pediatr Hematol Oncol*. 1990; 12: 95–104.
13. *Williams GD, Bratton SL, Nielsen NJ, Ramamoorthy C.* Fibrinolysis in pediatric patients undergoing cardiopulmonary bypass. *J Cardiothorac Vasc Anesth*. 1998; 12: 633–638.
14. *Kreuziger LB, Massicotte MP.* Adult and pediatric mechanical circulation: a guide for the hematologist. *Hematol Am Soc Hematol Educ Program*. 2018; 30: 507–515.
15. *Edmunds EL.* The blood-surface interface. *Gravlee GP, editor. Cardiopulmonary Bypass: Principles and Practice* 3 ed. Philadelphia, PA: Lippincott Williams & Wilkins (2008).
16. *Kreuziger LB, Massicotte MP.* Mechanical circulatory support: balancing bleeding and clotting in high-risk patients. *Hematol Am Soc Hematol Educ Program*. 2015: 61–68.
17. *Rosenthal DN, Almond CS, Jaquiss RD, Peyton CE, Auerbach SR, Morales DR et al.* Adverse events in children implanted with ventricular assist devices in the United States: data from the pediatric interagency registry for mechanical circulatory support (PediMACS). *J Heart Lung Transplant*. 2016; 35: 569–577.
18. *Sutor AH, Massicotte P, Leaker M, Andrew M.* Heparin therapy in pediatric patients. *Semin Thromb Hemost*. 1997; 23: 303–319.
19. *Severin T, Sutor AH.* Heparin-induced thrombocytopenia in pediatrics. *Semin Thromb Hemost*. 2001; 27: 293–299.
20. *Vakil NH, Kanaan AO, Donovan JL.* Heparin-Induced Thrombocytopenia in the Pediatric Population: A Review of Current Literature. *J Pediatr Pharmacol Ther*. 2012; 17 (1): 12–30.
21. *Avila L, Amiri N, Yenson P, Khan S, Zavareh ZT, Chan AKC et al.* Heparin-Induced Thrombocytopenia in a Pediatric Population: Implications for Clinical Probability Scores and Testing. *J Pediatr*. 2020; 226: 167–172.
22. *Kishimoto TK, Viswanathan K, Ganguly T, Elankumaran S, Smith S, Pelzer K et al.* Contaminated heparin associated with adverse clinical events and activation of the contact system. *N Engl J Med*. 2008; 358: 2457–2467.
23. *Bhandari M, Hirsh J, Weitz JI, Young E, Venner TJ, Shaughnessy SG.* The effects of standard and low molecular weight heparin on bone nodule formation in vitro. *Thromb Haemost*. 1998; 80: 413–417.

24. *Jones AJ, O'Mara KL, Kelly BJ, Samraj RS.* The impact of antithrombin III use in achieving anticoagulant goals in pediatric patients. *J Pediatr Pharmacol Ther*. 2017; 22: 320–325.
25. *Buck ML.* Bivalirudin as an alternative to heparin for anticoagulation in infants and children. *J Pediatr Pharmacol Ther*. 2015; 20: 408–417.
26. *Campbell CT, Diaz L, Kelly B.* Description of Bivalirudin Use for Anticoagulation in Pediatric Patients on Mechanical Circulatory Support. *Ann Pharmacother*. 2021; 55 (1): 59–64.
27. *Ghbeis MB, Vander Pluym CJ, Thiagarajan RR.* Hemostatic challenges in pediatric critical care medicine – hemostatic balance in VAD. *Front Pediatr*. 2021; 26: 625–632.
28. *Steiner ME, Bomgaars LR, Massicotte MP.* Berlin heart EXCOR pediatric VAD IDE study investigators antithrombotic therapy in a prospective trial of a pediatric ventricular assist device. *ASAIO J*. 2016; 62: 719–727.
29. *Sylvia LM, Ordway L, Pham DT, DeNofrio D, Kiernan M.* Bivalirudin for treatment of LVAD thrombosis: a case series. *ASAIO J*. 2014; 60: 744–747.
30. *VanderPluym CJ, Cantor RS, Machado D, Boyle G, May L, Griffiths E et al.* Utilization and outcomes of children treated with direct thrombin inhibitors on paracorporeal ventricular assist device support. *ASAIO J*. 2020; 66: 939–945.
31. *Miera O, Schmitt KL, Akintuerk H, Boet A, Cesnjevar R, Chila T et al.* Antithrombotic therapy in pediatric ventricular assist devices: Multicenter survey of the European EXCOR Pediatric Investigator Group. *Int J Artif Organs*. 2018 Jul; 41 (7): 385–392.
32. *Steiner ME, Bomgaars LR, Massicotte MP.* Antithrombotic therapy in a prospective trial of a pediatric ventricular assist device. *ASAIO J*. 2016; 62: 719–27.
33. *Peng E, Kirk R, Wrightson N, Duong P, Ferguson L, Griselli M et al.* An extended role of continuous flow device in pediatric mechanical circulatory support. *Ann Thorac Surg*. 2016; 102: 620–627.
34. *Rosenthal DN, Lancaster CA, McElhinney DB, Chen S, Stein M, Lin A et al.* Impact of a modified antithrombotic guideline on stroke in children supported with a pediatric ventricular assist device. *J Heart Lung Transplant*. 2017; 36: 1250–1257.
35. *O'Connor MJ, Lorts A, Davies RR, Fynn-Thompson F, Joong A, Maeda K et al*. Early experience with the HeartMate 3 continuousflow ventricular assist device in pediatric patients and patients with congenital heart disease: A multicenter registry analysis. *J Heart Lung Transplant*. 2020 Jun; 39 (6): 573–579.
36. *Andreas M, Moayedifar R, Wieselthaler G, Wolzt M, Riebandt J, Haberl T et al.* Increased thromboembolic events with dabigatran compared with Vitamin K antagonism in left ventricular assist device patients. *Circ Heart Fail*. 2017; 10 (5): 1–6.
37. *Parikh V, Parikh U, Ramirez AM, Lamba H, George J, Fedson S et al.* Novel oral anticoagulants in patients with continuous flow left ventricular assist devices. *J Heart Lung Transplant*. 2019; 38: S425.
38. *Schulte-Eistrup S, Mayer-Wingert N, Reiss N, Sindermann J, Warnecke H.* Apixaban in HVAD patients noncompliant to standard vitamin-k-antagonism. *J Heart Lung Transplant*. 2019; 38: S68.
39. *Li S, Mahr C.* Anticoagulation in the HeartMate 3 Left Ventricular Assist Device: Are We Finally Moving the Needle? *ASAIO J*. 2022; 68 (3): 323–324.
40. *Ghbeis MB, Vander Pluym CJ, Thiagarajan RR.* Hemostatic Challenges in Pediatric Critical Care Medicine – Hemostatic Balance in VAD. *Front Pediatr*. 2021; 9: 1–11.

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