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Developmental hemostasis: laboratory and clinical implications

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SUMMARY

The pediatric hemostatic balance, which is different from that in adults, is an evolving process as the hemostatic system changes and matures throughout the time from fetal to adult life, particularly in the first months of life. The concept of developmental hemostasis was confirmed by several studies evaluating different patients' population in various technical conditions. All these studies demonstrated that, at birth, the plasma levels of most coagulation factors were around half that found in adults, the preterm newborns having lower levels than full-term newborns. Adult values were usually reached between a few months of age and up to above 16 years for specific parameters. If the global trends are consistent across the studies, differences in absolute values could be demonstrated that are likely due to differences in the reagents and/or the instruments used. Accordingly, it is recommended by the Perinatal and Pediatric Haemostasis Subcommittee of the Scientific and Standardization Committee of the ISTH for each laboratory to define the age-dependent reference ranges using its own technical condition. The understanding of that concept of developmental hemostasis, which is now universally accepted, is critical to ensure optimal prevention, diagnosis, and treatment of thrombotic and hemorrhagic diseases in children. Actually, developmental hemostasis could affect the interaction between anticoagulant drugs and the coagulation system and so explain in part the discrepancy between anticoagulation in adults and in children. Finally, developmental hemostasis could probably provide a protective mechanism for neonates and children, contributing to the decreased risk of thrombosis and/or bleeding in these age-groups.

INTRODUCTION

The pediatric hemostatic balance is different from that in adults and is an evolving process. Actually, the hemostatic system changes and matures throughout the time from fetal to adult life, particularly in the early months of life [1–4], as demonstrated by several studies in various technical conditions. The understanding of the concept of developmental hemostasis, which is now universally accepted, is critical to ensure

optimal prevention, diagnosis, and treatment of thrombotic and hemorrhagic diseases in children.

DEVELOPMENTAL HEMOSTASIS

Hemostasis is a complex mechanism involving both procoagulant and anticoagulant factors. It ultimately enables the blood to remain liquid when circulating in intact vessels and to avoid both excessive bleeding by promoting clot formation after endothelial injury and excessive clotting by limiting clot formation to the site of injury. The hemostatic equilibrium depends on many parameters including platelets as well as clotting factors and inhibitors.

The pediatric hemostatic balance is different from that in adults, and children could not be considered just as miniature adults [1], at least for hemostasis. Moreover, it is an evolving process as shown by Andrew *et al.* [2–4] more than 20 years ago both in preterm and in full-term infants. These authors demonstrated that the hemostatic system changes and matures throughout the time from fetal to adult life, particularly in the first months of life, and promoted the concept of developmental hemostasis [5]. Actually, the coagulation factors from maternal origin are unable to cross the placental barrier [6], and the synthesis of clotting factors by the fetus starts during the fifth week of gestation for fibrinogen [7], its blood becoming clottable after eleven weeks [8]. Fetal reference ranges for coagulation parameters were studied for different gestational age-groups, and the median test results were between 10% and 30% of adult values, depending on the evaluated parameter, in fetuses between 19 and 23 weeks of gestation and progressively increased to levels between 10% and 50% in fetuses between 30 and 38 weeks of gestation [9, 10].

The seminal findings of Andrew *et al.* [2–4] were then confirmed by several studies evaluating different patients' population in various technical conditions [11–18]. The patients' selection criteria were relatively homogeneous among the studies, even if inclusion/exclusion criteria could be slightly different as well as their age grouping, as shown in Table 1. The main difference between studies relied on the number of evaluated patients in each age-group ranging from 10 to more than 500 individuals. The sampling process, which is a key point to take into account, as drawing blood from young infants or neonates could be more problematic than in adults, appeared to be comparable in the different studies with blood collected by venipuncture through 18-G to 24-G needles, depending of the age of the patients, into tubes containing 3.2% citrate (1 vol/9 vol) (Table 2). Even though differences were found concerning other pre-analytical steps such as the conditions of centrifugation (Table 2), the main source of heterogeneity among the studies concerned the analytical phase with multiple reagents/analyzers combinations (Table 3). Most of these studies mainly investigated activity assays for most parameters involved in the coagulation system [11–15, 17, 18]; however, one study only focused on the antigen concentrations of various analytes [16]. All demonstrated that, at birth, the plasma levels of most coagulation proteins were around half that measured in adults, the preterm newborns having lower levels than full-term newborns [2, 3]. Adult values were reached between a few months of age and up to above 16 years for specific parameters such as coagulation factor VII (Table 4). Whereas the global trends are consistent across the studies [2–4, 11–18], differences in absolute values could be demonstrated that are likely due to differences in the reagents and/or the instruments used to measure these parameters [15]. This could be particularly significant for global coagulation tests such as the prothrombin time (PT) or the activated partial thromboplastin time (aPTT) [15]. Accordingly, it is recommended by the Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) for each laboratory to define the age-dependent reference ranges using its own technical condition [19].

Primary hemostasis was far less studied. However, the platelet count is usually normal or elevated at birth, reaching adult values within 1 year after transient increases [20]. Despite hyporeactive platelets, particularly in the neonatal period [20–25], the bleeding time and the platelet closure time (PFA-100®) were found to be shortened in newborns and to normalize before the end of the first month of life [21, 22, 25]. Significantly higher levels of von Willebrand factor (VWF) were reported in newborns, which then decreased reaching adult values after 1 year of life, at a time where appears the significant increase in plasma levels in non-O blood groups *vs.* O blood group [26].

Table 1. Main studies defining reference ranges for hemostasis parameters in pediatric populations – main demographical characteristics of the studied populations

Parameter	Andrew *et al.* [2]	Andrew *et al.* [3]	Andrew *et al.* [4]	Flanders *et al.* [11, 12]	Monagle *et al.* [13]	Appel *et al.* [15]	Attard *et al.* [16]	Toulon *et al.* [17]
Age-groups	D1, D5, D30, D90, D180	D1, D5, D30, D90, D180	Y1–5, Y6–10, Y11–16	Y7–9, Y10–11, Y12–13, Y14–15, Y16–17	D1, D3, mo 1–12, Y1–5, Y6–10, Y11–16	mo 1–6, mo 7–12, Y1–5, Y6–10, Y11–18	D1, D3, mo 1–12, Y1–5, Y6–10, Y11–18	W2–4, mo 1–5, mo 6–12, Y1–5, Y6–10, Y11–17
n subjects/ age-group	52–77	24–70	20–50	150–245	20–71	25–37	10–20	36–511
Gestational age	≥37 GW	30–36 GW	N Appl.	N Appl.	>37 GW	Full-term	>37 GW	ND
Weight at birth (g)	3500 ± 1064 g	2160 ± 350 g (30–33 GW) 1730 ± 350 g (34–36 GW)			≥2500 g	>3000 g	≥2500 g	ND
APGAR at 5 min	≥7	≥7			≥7	ND	≥7	ND
VK	Yes (1 mg IM)	Yes (1 mg IM)			Yes (1 mg IM)	Yes (40 μg/100 g)	Yes (1 mg IM)	Yes (2 mg orally)
Inclusion criteria	Healthy full-term infants	Healthy premature infants	Healthy children Before elective day surgery	Healthy children Before surgery	Healthy children Before minor day surgery	Healthy full-term infants	Healthy children Before minor day surgery	Healthy children Before minor day surgery
Exclusion criteria	Any postnatal problem	ARDS, sepsis, perinatal asphyxia, O2 support, ventilation	Personal or family history of bleeding	History of thrombosis or bleeding Any medication	History of thrombosis or bleeding Anticoagulant therapy	Personal history of thrombosis or bleeding Anticoagulant therapy	History of thrombosis or bleeding Anticoagulant therapy	Personal or family history of thrombosis or bleeding Anticoagulant therapy

D: day; mo: month; W: week, Y: year; ARDS, acute respiratory distress syndrome; GW, gestational week; N Appl., not applicable; ND, not determined; VK, vitamin K.

Table 2. Main studies defining reference ranges for hemostasis parameters in pediatric populations – pre-analytical parameters

Parameter	Andrew *et al.* [2]	Andrew *et al.* [3]	Andrew *et al.* [4]	Flanders *et al.* [11, 12]	Monagle *et al.* [13]	Appel *et al.* [15]	Attard *et al.* [16]	Toulon *et al.* [17]
Needle	21 G	21 G	ND	ND	21–23 G	18–24 G	ND	21–23 G
Citrate concentration	3.2%	3.2%	3.2%	3.2% (1 vol/9 vol)	3.2% (0.106 M) (1 vol/9 vol) S-Monovette (Sarstedt)	3.2% (0.105 M) (1 vol/9 vol)	3.2%(0.106 M) (1 vol/9 vol)	3.2% (0.109 M) (1 vol/9vol)
Centrifugation	1700 ***g***	1700 ***g***	1700 ***g***	3000 ***g***, RT, 20 min	3000 ***g***, +10 °C, 10 min	2500 ***g***, RT, 15 min, then 10 000 ***g***, RT, 5 min	1450 ***g***, +10 °C, 10 min	2000–2500 ***g***, +18 °C, 15 min (×2)
Freezing conditions	Yes (ND)	Yes (ND)	Yes (ND)	Yes (−80 °C)	Yes (−85 °C)	Yes (−70 °C)	Yes (−80 °C)	Yes (−80 °C)

ND: not determined, RT: room temperature.

CLINICAL IMPLICATIONS

The understanding of that concept of developmental hemostasis is critical to ensure optimal prevention, diagnosis, and treatment of thrombotic and hemorrhagic diseases in children. Actually, developmental hemostasis could probably provide a protective mechanism for neonates and children, contributing to the decreased risk of thrombosis and/or bleeding in these age-groups [27]. However, when such an event happens, it is not unlikely that the usually decreased plasma levels of coagulation factors or inhibitors could have had a triggering effect. In addition, developmental hemostasis could affect the interaction between anticoagulant drugs and the coagulation system and so explain in part the discrepancy between anticoagulation in adults and in children. Finally, these low levels of proteins involved in the coagulation could be an additional difficulty for the diagnosis and the treatment of such thrombotic or hemorrhagic complications.

Treatment of thrombotic complications

Anticoagulation in children remains a challenge, given the lack of robust evidence-based recommendations [28]. Actually, due to the paucity of data, particularly in neonates, most of the recommendations from the American College of Chest Physicians (ACCP) are only grade 2C [29]. In addition to differences with adults in term of physiology, as previously discussed, the pharmacological response to antithrombotic drugs, epidemiology, and long-term consequences of thrombosis are also different [29]. The common treatment options for venous thromboembolism (VTE) in the pediatric population include unfractionated heparin (UFH), low molecular weight heparin (LMWH) derivatives, and vitamin K antagonists (VKA) like warfarin. Other alternatives could include bivalirudin, argatroban, and fondaparinux in some specific situations [30], as well as the new direct oral anticoagulants (DOAC). However, most are used off-label [31] and pediatric dosages are derived from those in adults.

Unfractionated heparin is still widely used in pediatric patients requiring anticoagulant therapy [32]. The required UFH dosage is usually higher in neonates and younger children than in older ones or

Table 3. Main studies defining reference ranges for hemostasis parameters in pediatric populations—analytical parameters for the main studied parameters (analyzers, reagents, and current manufacturers)

Parameter	Andrew *et al.* [2]	Andrew *et al.* [3]	Andrew *et al.* [4]	Flanders *et al.* [11, 12]	Monagle *et al.* [13]	Appel *et al.* [15]	Attard *et al.* [16]	Toulon *et al.* [17]
Analyzer	ACL (IL)	ACL (IL)	ACL (IL)	STA-R (Stago) *BCS (Siemens)	STA Compact (Stago)	BCS (Siemens) CA-1500 (Sysmex)	Microplate reader	ACL TOP 700/ 500 (IL)
PT	Thromborel S (Siemens)	Thromborel S (Siemens)	Thromborel S (Siemens)	Neoplastin CI+ (Stago)	Neoplastin CI (Stago)	Thromborel S (Siemens) Dade Innovin (Siemens)	ND	HemosIL RecombiPlasTin 2G (IL)
aPTT	Actin FS (Siemens)	Actin FS (Siemens)	Actin FS (Siemens)	STA-PTT A (Stago)	STA-PTT A (Stago) CK Prest (Stago) Actin FS (Siemens) Platelin L (Organon Teknika)	Pathromtin SL (Siemens) Dade Actin FS (Siemens)	ND	HemosIL APTT SP (IL) HemosIL SynthASil (IL)
Fibrinogen	Not specified			STA-Fibrinogen (Stago)	STA-Fibrinogen (Stago)	Multifibren U (Siemens)	ND	HemosIL Fibrinogen C (IL) HemosIL QFA (IL)
Clotting factors	OSA/in house and commercial deficient plasmas	OSA/in house and commercial deficient plasmas	OSA/in house and commercial deficient plasmas	OSA/ deficient plasmas (HRF Inc)	OSA/ STA-deficient plasmas (Stago)	OSA/deficient plasmas (Siemens)	ELISA Asserachrom (Stago) Affinity Bioogicals	OSA/ HemosIL Deficient plasmas (IL)
Antithrombin	Ag (RID)	Ag (RID)	Chromogenic Ag (RID)	STA-Stachrom ATIII (chromogenic, Stago)	Chromogenic: Stachrom ATIII (chromogenic, Stago)	Innovance Antithrombin (chromogenic, Siemens) Behrichrom Antithrombin III (chromogenic, Siemens)	ND	HemosIL Liquid Antithrombin (chromogenic, IL)

(continued)

Table 3. (Continued)

Parameter	Andrew *et al.* [2]	Andrew *et al.* [3]	Andrew *et al.* [4]	Flanders *et al.* [11, 12]	Monagle *et al.* [13]	Appel *et al.* [15]	Attard *et al.* [16]	Toulon *et al.* [17]
Protein C	Asserachrom Protein C (ELISA, Stago)	Asserachrom Protein C (ELISA, Stago)	Chromogenic (Siemens) Asserachrom Protein C (ELISA, Stago)	Staclot Protein C (clotting, Stago)	Stachrom Protein C (chromogenic, Stago) Staclot Protein C (clotting, Stago)	Protein C Reagenz (clotting, Siemens) Behrichrom Protein C (chromogenic, Siemens)	ELISA (Affinity Bioogicals) Asserachrom Protein C (ELISA, Stago)	HemosIL Protein C (chromogenic, IL) HemosIL ProClot (clotting, IL)
Protein S	Total Ag (IEP)	Total Ag (IEP)	Total and free antigen (ELISA, Affinity Biologicals)	Staclot Protein S (clotting, Stago)	Staclot Protein S (Clotting, Stago)	Protein S Ac (Siemens)	Asserachrom free/total Protein S (ELISA, Stago)	HemosIL Protein S Activity (clotting, IL) HemosIL Free Protein S (latex agglutination, IL)
D-dimer	ND	ND	ND	ND	STA-Liatest D-dimer (latex agglutination, Stago)	Innovance D-dimer (Siemens)	ND	HemosIL D-dimer HS 500 (latex agglutination, IL)

(continued)

Table 3. (Continued)

Parameter	Andrew *et al.* [2]	Andrew *et al.* [3]	Andrew *et al.* [4]	Flanders *et al.* [11, 12]	Monagle *et al.* [13]	Appel *et al.* [15]	Attard *et al.* [16]	Toulon *et al.* [17]
VWF	Asserachrom VWF (ELISA, Stago)	Asserachrom VWF (ELISA, Stago)	Asserachrom VWF (ELISA, Stago)	STA-Liatest WWF:Ag (latex agglutination, Stago) *BC von Willebrand (VWF:RCo, Siemens)	ND	BC von Willebrand (VWF:RCo, Siemens)	ND	HemosIL von Willebrand Factor Ristocetin Cofactor Activity (IL) HemosIL von Willebrand Factor Activity (latex agglutination, IL) HemosIL von Willebrand Factor Antigen (latex agglutination, IL)
Plasminogen	unspecified	unspecified	Chromogenic Stago	STA-Stachrom Plasminogen (chromogenic, Stago)	ND	Behrichrom Plasminogen (chromogenic, Siemens)	ELISA (Affinity Biogicals)	HemosIL Plasminogen (chromogenic, IL)
Miscellaneous	HCII, alpha 2 macroglobulin, alpha 2 antiplasmin, alpha 1 antitrypsin, HMWK, PK, FXIII, thrombin clotting time	HCII, alpha 2 macroglobulin, alpha 2 antiplasmin, alpha 1 antitrypsin, HMWK, PK, FXIII, thrombin clotting time	HCII, alpha 2 macroglobulin, alpha 2 antiplasmin, alpha 1 antitrypsin, HMWK, PK, FXIII, bleeding time tPA, PAI-1	Alpha 2 antiplasmin	Free and total TFPI thrombin clotting time	Alpha 2 antiplasmin FXIII, thrombin clotting time, thrombin clotting time, batroxobin time		FXIII

Ag, antigen (assay); aPTT, activated partial thromboplastin time; ELISA, enzyme-linked immunosorbent assay; IEP, immunoelectrophoresis; IL, Instrumentation Laboratory; ND, not determined; OSA, one-stage (clotting) assay; PT, prothrombin time; RID, radial immunodiffusion; VWF, von Willebrand Factor. *Assay performed in the BSC analyzer.

Table 4. Coagulation parameters in neonatal and childhood *vs*. adult. Summary of test results and potential effect on hemostasis. For details, see Developmental hemostasis part

Component	Parameter	Neonatal period (mean value)*	Normalization	Net effect on hemostasis
Primary hemostasis	Platelets	Normal or increased	1 year (after transient increases)	Enhanced primary hemostasis
	von Willebrand factor	Increased (153%)*	3 months	
	Platelet closure time (PFA-100®)	Shortened	2–4 weeks	
Coagulation	FII, FVII, FIX, FX	Decreased (40–66%)*	1 year (up to 16 year for FVII)	Decreased coagulation potential
	FXI, FXII, PK, HMWK	Decreased (37–54%)*	1 year	
	FV	Normal or decreased (70%)*	1 year (up to 16 year)	
	FVIII	Normal or increased (100%)*	1 month	
	Fibrinogen	Decreased ** or normal	1 year	
	PT	Prolonged or normal	1 year	
	aPTT	Prolonged	1 year (up to 16 year)	
Natural coagulation inhibitors	Antithrombin	Decreased (63%)	3 months	Decreased regulatory/ inhibitory potential
	Protein C	Decreased (35%)	16 years	
	Protein S	Decreased (36%)*	3 months	
Fibrinolysis	Plasminogen	Decreased (36%)*	6 months	Increased fibrinolytic activity
	Alpha 2 antiplasmin	Normal or decreased (85%)*	6 months	
	tPA	Increased	1 week	
	D-dimer	Increased	16 years	

*In percentage (%) of adult values, from Andrew *et al.* [2].
**Fetal fibrinogen may be present.

Table 5. Main antithrombotic drugs used in pediatric patients, and hemostasis test results used to monitor their efficacy with their therapeutic range, when available

Drugs	Monitoring of treatment and hemostasis test used
Antiplatelet agents, for example, aspirin, or clopidogrel	Usually not required If needed: platelet aggregation study, PFA-100, or flow cytometry (P2Y12 inhibition for thienopyridines)
Unfractionated heparin	Anti-Xa activity between 0.35 and 0.70 IU/mL
Low molecular weight heparin derivatives	Usually not required If needed: anti-Xa activity between 0.50 and 1.00 IU/mL (sample taken 4 h after a SC injection)
Vitamin K antagonists	INR = 2.5 (between 2.0 and 3.0)
Direct oral anticoagulants, for example, dabigatran, rivaroxaban, apixaban	Usually not required If needed specific assays for dabigatran (dilute thrombin time or chromogenic assay) or for anti-Xa drugs (chromogenic assay)

INR, international normalized ratio; IU/mL, international unit per mL; SC, subcutaneous.

adults [29]. Thus, apparent heparin resistance of the newborn could be multifactorial, due to the low AT level, which is counterbalanced in physiological condition by higher plasma level of alpha 2-macroglobulin [2–4], and to an increased volume of distribution, as demonstrated in an animal model [33]. In addition, UFH effects, which were lower in infants when compared with older children, were more pronounced at low- than at high-dose regimen of UFH, the influence of age on UFH effect appearing to be dose-dependent [34]. Therapeutic treatments with UFH should be preferably monitored using anti-FXa activity, with test results between 0.35 and 0.70 International Units (IU)/mL [29], rather than using the aPTT that could be physiologically prolonged in the younger patients [35]. However, in older pediatric patients treated with full dose of UFH for cardiac catheterization, anti-FXa activity, aPTT, and even activated clotting time correlated well with UFH dose, reflecting a significant UFH dose–test result relationship, but with a poor agreement between the different test results [34].

Today, the treatment of choice of VTE in children has become LMWH derivatives, particularly in the case of provoked episodes as the duration of anticoagulation is limited. Advantages over other drugs and particularly VKA are multiple, including less frequent monitoring, no drug or food interactions, and acceptable efficacy and safety profiles. In addition, LMWH derivatives are also widely used in the treatment of pediatric arterial thrombosis and various other situations where thromboprophylaxis be required [31]. Even if the volume of distribution of the LMWH derivative enoxaparin was found similar in newborn and adult pigs [36], dose requirement for the LMWH derivative enoxaparin is usually higher in children, with age-specific dosages [37]. When targeting anti-FXa activity ranges, younger patients required higher doses of enoxaparin on a per-kg basis than older children, that is, 1.5 or eventually 1.7 or even 2.0 mg/kg in infants *vs*. 1.0 mg/kg in older children or in adults [28, 29, 37, 38]. The same applied for tinzaparin administered once daily with recommended daily dosages of 280 IU/kg between 0 and 2 months, 245 IU/mL between 2 and 12 months, 240 IU/kg between 1 and 5 years, 200 between 5 and 10 years, and 175 IU/kg (adult dosage) between 10 and 16 years [39]. In neonates, it is suggested that treatments with LMWH derivatives once or twice daily be monitored to a target anti-FXa activity range of 0.50–1.00 IU/mL in a sample taken 4–8 h after subcutaneous injection or 0.50–0.80 IU/mL in a sample taken 2–6 h after subcutaneous injection (grade 2C) [29].

It was suggested for children receiving VKA that the drug be monitored to a target international normalized ratio (INR) of 2.50 (range 2.00–3.00), except in the setting of prosthetic cardiac valves where the target value could be higher, as it is usual for adults [29]. It was suggested that INR should be measured using point-of-care monitors where resources make this possible (grade 2C) [29]. If up to now, warfarin was the only approved oral drug, the main limitations for its use was the requirement for regular monitoring and the high number of drug interaction, suggesting that an oral agent without frequent monitoring would be optimal for pediatric patients.

The DOACs, such dabigatran, rivaroxaban, apixaban, or edoxaban, are currently not registered in Europe or in the United States for pediatric patients. However, some off-label studies were published [40–44]. However, as too few data were published, no recommendations or even suggestions are available so far, even though there is an increasing need for new anticoagulation options in pediatric populations. None of the current DOAC have Food and Drug Administration (FDA)-approved indications and dosing in children. The two classes of DOACs and the drugs they are comprised of are factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and direct thrombin inhibitor (dabigatran). Off-label usage of these agents is largely based on adult doses. Until now, rivaroxaban and dabigatran have the most published data and ongoing trials in pediatric patients compared with apixaban and edoxaban [44]. After evaluating the current literature available on these agents, it is, however, still too early to make any definitive recommendations on their usage in this specific population.

The literature is scarcer about the use of antiplatelet agents in pediatric patients. When aspirin is used as an antiplatelet agent, it is suggested to use doses of 1–5 mg/kg/day (grade 2C) [29]. Concerning the other antiplatelet drugs, the common dosages are dipyridamole 2–5 mg/kg/day and clopidogrel 0.2 mg/kg/day (rounded to one quarter or one half tablet containing 75 mg [45].

An extensive review of the literature concerning the use of antithrombotic drugs in neonates and

children was reported in the 9th Edition of the ACCP Evidence-Based Clinical Practice Guidelines [29]. The Main antithrombotic drugs used in pediatric patients, and hemostasis test results used to monitor their efficacy with their therapeutic range, when available, are reported in the (Table 5).

Bleeding complications

If the hemostatic balance of newborns and children are different from that of adults, the system is effective and they do not usually suffer from spontaneous bleeding complications. However, the risk of bleeding during childhood could be increased, when compared to older individuals, when children present with either congenital or acquired hemostatic abnormalities. Severe congenital bleeding disorders, quite infrequent, could lead to hemorrhage in the newborns particularly in the case of hemophilia A or B [46]. Vitamin K deficiency [47], disseminated intravascular coagulation (DIC), and liver diseases are among the most frequent acquired causes of neonatal bleeding [27, 48]. Usually, the clinical presentation of bleeding disorders in infants is characterized by one or more of the following symptoms: cephalohematomas and intracranial hemorrhage, injury-related bleeding, and skin bleeding such as petechiae, purpura, and ecchymoses [46]. Other presentations could be joint bleed within the first year of life that is typical of severe hemophilia A and B, and persistent oozing from the umbilical cord at day 8 that is typical for severe factor XIII deficiency [46]. Particularly in newborns, finding a diagnosis could be difficult due to physiological prolonged global assays, such as the aPTT, and to low levels of coagulation factors [49]. Actually, severe hemophilia A or von Willebrand disease (VWD) can usually be diagnosed at birth or during the first days of life, as the plasma levels of factor VIII or VWF at birth are either similar to or even higher than adult values [50]. The diagnosis of hemophilia B could be more problematic, as the plasma levels of FIX was decreased at birth, particularly in preterm newborn, which could lead to false diagnosis of hemophilia B, and the same applied to milder clotting factor deficiency [50].

So, bleeding in children can be a diagnostic challenge because of the wide range of possible causes, even though making a specific diagnosis is clinically important in order to provide appropriate therapy. Besides a detailed physical examination, the evaluation of a child presenting with a bleeding episode should include a comprehensive medical and bleeding history and a complete family history. In addition, selected laboratory tests should be prescribed, as the bleeding disorder, which could be inherited or acquired, could be related to, for example, clotting factor deficiency, low platelet count, platelet dysfunction, or VWD [51]. The precise diagnostic is critical to ensure treatment of the bleeding episode or prevention of excessive bleeding in the case of surgical procedure. This could include platelet transfusion in the case of thrombocytopenia or platelet function defects [52], the use factor concentrate in the case of hemophilia or most of the other single factor deficiency [53]. Desmopressin (DDAVP), a synthetic form of vasopressin that acts to stimulate the release of VWF from endothelial cells, is often used in case of mild VWD [54–57]. However, its antidiuretic property, which is an important but rare side effect of its use [58], limits its administration particularly in children younger than 3 years [59].

CONCLUSIONS

Understanding of the concept of developmental hemostasis, which is now universally accepted, is critical to ensure optimal prevention, diagnosis, and treatment of hemorrhagic and thrombotic diseases in children. As a consequence, it became mandatory for the laboratory that age-specific reference ranges for coagulation parameters should be used. Actually, it seems impossible to ask each laboratory to establish its own references intervals for all coagulation parameters in its own technical conditions [19] by testing at least 120 healthy individuals in each age-group, as it is recommended by the CLSI Guideline EP 28-A3C [60]. So, the best option for a laboratory would be to translate the findings of the literature to local reference ranges for neonates and children, by taking into account their specific technical environment. In that respect, data are already available for reagents and analyzers from the main manufacturers, that is, by alphabetic order, Instrumentation Laboratory [17], Siemens [15], and Stago [11–13]. In the case of newcomers, specific, and preferably multicentre, studies would have to be carried out in order to establish the specific pediatric reference ranges using these new reagents/analyzers combinations.

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