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RECOMMENDATIONS

Unresolved issues concerning venous thromboembolism. Venous thromboembolism in children. Consensus of the French Society of Vascular Medicine (SFMV)

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Summary Venous thromboembolism (VTE) rarely occurs during childhood and, with few exceptions, should be considered as a disease of sick children. Current recommendations concerning the duration of anticoagulant treatment for paediatric VTE are essentially based on the results of clinical trials conducted in adults. Yet the underlying medical conditions, incidence, and anatomical locations of the disease, as well as the rates of unprovoked VTE, morbidity, and mortality, differ between adults and children. Unprovoked VTE is uncommon in childhood. Most children experiencing VTE present risk factors, such as the presence of a central venous catheter (CVC), cancer, chemotherapy (in particular with asparaginase or steroids), obesity, severe infection, congenital cardiopathy (notably in conjunction with hepatic venous stasis), serious trauma, an anatomical venous anomaly (such as atresia or agenesia) or a nephrotic syndrome (inducing a deficit in antithrombin or protein S), premature birth, or maternal combined oral contraception. The recent possibility of administering direct oral anticoagulants (DOAC) to children undoubtedly constitutes the greatest change in the treatment of paediatric VTE. The advantages of this therapy include the possibility of its oral administration, even in infants, the absence of any need for laboratory follow-up, and the lack of food interactions. With the approval of the

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direct factor Xa inhibitor rivaroxaban (by the European Medicines Agency and Health Canada), and the direct thrombin inhibitor dabigatran (by the European Medicines Agency and the US Food and Drug Administration), paediatric anticoagulant therapy is changing. Only rivaroxaban currently has a Marketing Authorisation in France for the treatment of childhood VTE.

Context

Venous thromboembolism (VTE) is a rare event in childhood (with an estimated annual incidence of 0.07 to 0.14/10,000 children). With few exceptions, it should be considered as a disease of sick children (in whom the incidence reaches 100 to 1000/10,000 children, or > 58 per 10,000 hospitalisations) [1,2]. Even though we consider thrombosis as a single entity in this section, paediatric thrombosis in fact covers a broad spectrum of locations, in each of which VTE may be considered as a rare disease.

Current recommendations concerning the duration of anticoagulant treatment in the case of paediatric VTE is principally based on the results of studies conducted in adults [3]. Yet the underlying medical conditions, frequency, and anatomical locations of VTE, as well as the rates of unprovoked events, morbidity, and mortality, are not the same in adults and children.

Unprovoked VTE is rare in childhood. The majority of children experiencing VTE present risk factors, such as the presence of a central venous catheter (CVC), cancer, chemotherapy (particularly with asparaginase or steroids), obesity, severe infection, congenital heart disease (notably in conjunction with hepatic venous stasis), serious trauma, an anatomical venous anomaly (such as atresia or agenesia), a nephrotic syndrome (inducing a deficit in antithrombin or protein S), premature birth, or maternal use of a combined oral contraception [3].

The recent possibility of administering direct oral anticoagulants (DOAC) to children is undoubtedly the greatest change in the treatment of paediatric VTE. The advantages of this therapy include the possibility of oral administration, even to infants, the absence of any need for laboratory monitoring, and the lack of food interactions. With the approval of the direct factor Xa inhibitor rivaroxaban (by the European Medicines Agency and Health Canada), and the direct thrombin inhibitor dabigatran (by the European Medicines Agency and the US Food and Drug Administration), paediatric anticoagulation is changing. At present, only rivaroxaban has a Marketing Authorisation for the treatment of paediatric VTE in France.

Tools and recommendations: literature review

Diagnosis

The signs and symptoms of VTE are just as nonspecific in children as in adults and no clinical probability score has yet been validated in the former population. Probably owing to the major differences in epidemiology, notably including a much higher incidence of provoked events in children, the scores generally used for the adult population have not been validated in the paediatric context [4,5].

A study in 27 children showed a high d-dimer diagnostic sensitivity, but a more modest specificity with variations in the positivity limits [6]. Only one study in 519 children, published in 2012, proposed six criteria for estimating the clinical probability of VTE: septicaemia, presence of a CVC, direct admission to a resuscitation or intensive care unit, hospitalisation for > 7 days, immobilisation for > 72 hours, and maternal use of combined oral contraception [7].

Diagnosis based on an ultrasound examination should be preferred for all accessible sites, namely lower and upper limbs, neck, and abdomen. Angiography or scintigraphy is the examinations of choice for the diagnosis of pulmonary embolism. Intracardiac thromboses at the extremity of the implantable site may also be detected by echocardiography.

Etiology

The presence of a CVC represents over 90% of the causes of neonatal VTE [5,6] and over 50% of those of paediatric VTE [7]. The onset of a catheter-related thrombosis in neonates does not necessitate a search for hereditary thrombophilia.

The cancers most frequently associated with VTE are lymphomas, followed by leukaemias [8]. Insertion of a CVC is implicated in over 50% of cases [9].

Thromboses have also been observed in patients presenting major thalassaemia, with a prevalence of 1.1 to 4% [10].

In patients who exhibit both proximal and distal VTE in the absence of any provoking factor, or whose family includes other members with a history of thrombosis, a search for biological factors conducive to thrombophilia should be undertaken. This exploration should comprise, in the first instance, a search for anti-β2-glycoprotein (GP)-1 antibodies, anticardiolipin antibodies, and lupus anticoagulants, a search for antithrombin, protein C, and protein S deficits, and a search for a Leiden mutation in factor V or a prothrombin mutation. In a second step, depending on the context, a search for nocturnal paroxysmal haemoglobinuria, and haemoglobin electrophoresis should be performed.

If no acquired provoking factor can be identified, or if other family members have experienced thrombosis, a search for thrombophilia is indicated. This should comprise:

- in the first instance, a search for anti-β2-glycoprotein (GP)-1 antibodies, anticardiolipin antibodies and lupus anticoagulant should be undertaken, as well as a search for antithrombin, protein C and protein S deficits, a Leiden mutation of factor V, or a prothrombin mutation;

- in a second step, depending on the context, a search for nocturnal paroxysmal haemoglobinuria, and a haemoglobin electrophoresis should be performed.

Treatment

The treatment of paediatric VTE is based on the use of heparins (unfractionated heparin [UFH], a low-molecular-weight heparin [LMWH]), a vitamin K antagonist (VKA) and more recently, a direct oral anticoagulant (DOAC).

The initial treatment often comprises administration of UFH or LMWH during at least the first five days. With respect to DOAC, only rivaroxaban currently has a Marketing Authorisation in France for the treatment of VTE in children. The weight of the child should be monitored, and the dose reappraised regularly, particularly in the case of children weighing less than 12 kg, to ensure maintenance of a therapeutic dose.

Unfractionated heparin

UFH is used for children presenting haemodynamic instability, an immediate risk of bleeding, or severe renal insufficiency. The routes of administration are the same as for adults (intravenous or sub-cutaneous). As in adults, the Activated partial thromboplastin time (APTT) or the anti-Xa activity should be monitored at least once a day as well as 4—6 hours after each change in dose. The therapeutic window is derived from that determined in adults: anti-Xa activity 0.35—0.7 IU/mL or the APTT range corresponding to these limits. The use of UFH carries a risk of heparin-induced thrombocytopenia (HIT) and osteoporosis, which should be taken into account: the duration of UFH treatment should be as short as possible. Maintenance doses of UFH depend on the patient's age, infants requiring the highest doses (on average 28 IU/kg/h). The mean doses of UFH needed for older children are similar to those used for adults (18 IU/kg/h) [11].

A nomogram for adjusting UFH doses of UFH in children is presented in Table 1 [12]. Bolus administration in children remains controversial: boluses of 75 to 100 IU/kg induced an excessive prolongation of APPT during more than 100 minutes. In practice, many clinicians either administer small boluses of 50 IU/kg or refrain from bolus use, notably in children at risk of bleeding [11].

The rate of bleeding during UFH treatment is less than 1%, this complication being frequently due to overdose, notably in newborns [13]. Precautions to avoid errors in dilution or infusion rate are particularly important.

Low-molecular weight heparins

LMWH constitute the first-choice treatment for the acute phase of paediatric VTE, as they can be administered subcutaneously and carry a lower risk of HIT. However, the predictability of anticoagulant activity with the use of body-weight-adjusted doses is lower than in adults, probably owing to differences in binding to plasma proteins. The initial LMWH doses recommended are presented in Table 2 [14].

The response to LMWH is highly variable in children. Anticoagulant activity is generally checked 4 to 6 hours after dose administration, even though no study has demonstrated a correlation between the dose administered and the risk of thrombosis or bleeding [11]. The therapeutic dose ranges from 0.5 to 1.2 IU/mL, and the prophylactic dose from 0.2 to 0.4 IU/mL (based on studies in adults).

In most studies, LMWH were monitored once or twice a day for as long as the anti-Xa activity remained outside the therapeutic range, then once a week. No study has demonstrated the value of monitoring anti-Xa activity during treatment with LMWH, with respect to either efficacy or safety. It has nevertheless been reported that dosing errors are less common when prescriptions are expressed in terms of IU/kg [15].

The frequency of major bleeding ranges from 0 to 19%. No data are available concerning the incidence of osteoporosis (although cases have been reported after prolonged use of LMWH, particularly in premature newborns), HIT, or other hypersensitivity reactions in children exposed to LMWH. Cases of reversible alopecia have also been described.

Vitamin K antagonists

VKA are rarely used in young children for various reasons (vitamin K level lower than that in adults, consumption of formula milk enriched in vitamin K, lack of pharmaceutical forms other than tablets, although customised preparations in drinkable form may be prescribed).

The most widely employed VKA is warfarin. The use of warfarin in the paediatric population has been validated in only one study, the REVIVE TRIAL, including 36 patients, published in 2003 [16]. The therapeutic International Normalized Ratio (INR) range for children with VTE is 2 to 3, as for adults. Warfarin is generally started at a dose of 0.1 to 0.2 mg/kg [14]. Patients presenting hepatic insufficiency require lower doses. A nomogram for guiding prescription is presented in Table 3 [14].

The use of VKA to treat VTE is generally avoided in paediatrics, when the duration of treatment is 6 weeks to 3 months.

VKA are difficult to manage owing to their tablet formulation, food interactions, and the need for frequent laboratory monitoring. The requirement for VKA changes rapidly during infancy owing to rapid evolution of the physiological values of vitamin-dependent coagulation proteins and changes in food habits. Furthermore, little information is available concerning the specific efficacy or innocuity of VKA use in neonates.

In children of school age, a monitoring schedule similar to that used for adults may be envisaged: initially several time a week and then, if the INR remains stable, at longer intervals, but not less than once a month.

INR monitors designed for patient use have proved to be easy to handle and reliable, besides improving quality of life. These devices are reimbursed in France for patients up to 18 years of age. Since 2008, their reimbursement has been conditional on the training of children and their caregivers in their use. Equilibration of the INR is correlated with the quality of life of children receiving VKA [17].

Table 1 Nomogram for UFH dose adjustment in children [11].

Age	Infusion rate	Anti-Xa target	Control	Adaptation
< 1 year	28 IU/kg/h	0.35 to 0.70 U/mL	Hour 4	10%
> 1 year	20 IU/kg/h	0.35 to 0.70 U/mL	Hour 4	10%

Table 2 Initial LMWH doses recommended for children [11].

LMWH	Age or body weight	Therapeutic dose	Prophylactic dose
Enoxaparin	≤ 2 months	150 IU/kg/12 h	75 IU/kg/12 h
	> 2 months	100 IU/kg/12 h	50 IU/kg/12 h
	20 to 40 kg	100 IU/kg/12 h max. 10,000 IU/12 h	2000 IU/24 h
	40 to 80 kg	100 IU/kg/12 h max. 10,000 IU/12 h	4000 IU/24 h
Tinzaparin	≤ 2 months	275 IU/kg once a day	75 IU/kg once a day
	2—12 months	250 IU/kg once a day	75 IU/kg once a day
	1—5 years	240 UI/kg once a day	75 IU/kg once a day
	5—10 years	200 IU/kg once a day	75 IU/kg once a day
	10—16 years	175 IU/kg once a day	50 IU/kg once a day
Dalteparin	≤ 2 months	150 IU/kg twice a day	150 UI/kg once a day
	> 2 months	100 IU/kg twice a day	100 IU/kg once a day

Table 3 Nomogram for VKA dose adjustments in children [14].

INR	Initial dose — adjustment	
Day 1	1.0—1.3	0.1—0.2 mg/kg orally (maximum 5 mg)
Days 2—4	1.1—1.3	Repeat the initial dose
	1.4—1.9	50% of the initial dose
	2.0—3.0	50% of the initial dose
	3.1—3.5	25% of the initial dose
	> 3.5	Suspend treatment for as long as the INR is > 3.5 then restart at 50% of the initial dose
Maintenance	1.1—1.4	Increase the dose by 20%
	1.5—1.9	Increase the dose by 10%
	2,0—3.0	No change
	3.1—3.5	Reduce the dose by 10%
	> 3.5	Suspend treatment for as long as the INR is > 3.5 then restart at 20% decreased dose

Bleeding is the principal complication of VKA treatment. The rate of bleeding events during well equilibrated treatment is less than 0.5% per year, but around 30% of young girls report metrorrhagia. Other possible complications include a decrease in bone density in the case of treatment lasting more than one year. In rare cases, hair loss has been described.

We advise against initiating VKA treatment in children with VTE if the likely duration of treatment is less than 3 months. For prolonged treatment, alternative therapeutic options, notably DOAC, should be considered in all cases.

Direct oral anticoagulants (DOAC)

DOACs have several advantages that make them a good option for children, including the availability of oral formulations, predictable pharmacokinetics, and the absence of food interactions. Two DOACs now have a Marketing Authorisation for the treatment of paediatric VTE, namely rivaroxaban and dabigatran.

Rivaroxaban: EINSTEIN Junior, a controlled, randomised, phase III trial, investigated the safety and efficacy of rivaroxaban compared to those of heparins or VKA in children presenting acute VTE [18]. This was an open, descriptive study, without a pre-defined population size and consequently with no formulated statistical hypothesis. It included 500 patients: 51% presenting VTE, 25% CVC-related thrombosis, and 23% central venous thrombosis. A transient and/or permanent provoking factor was identified in 87% of

Table 4 Nomogram of recommended doses of rivaroxaban for children (1 mg of rivaroxaban = 1 mL of suspension) [19].

Body weight (kg)		Rivaroxaban dosing schedule			Total daily dose	Adapted blue syringe
Min	Max	Once a day	Twice a day	3 times a day		
2.6	< 3			0.8 mg	2.4 mg	1 mL
3	< 4			0.9 mg	2.7 mg	1 mL
4	< 5			1.4 mg	4.2 mg	5 mL
5	< 7			1.6 mg	4.8 mg	5 mL
7	< 8			1.8 mg	5.4 mg	5 mL
8	< 9			2.4 mg	7.2 mg	5 mL
9	< 10			2.8 mg	8.4 mg	5 mL
10	< 12			3.0 mg	9.0 mg	5 mL
12	< 30		5 mg		10.0 mg	5 mL or 10 mL
30	< 50	15 mg			15.0 mg	10 mL
≥ 50		20 mg			20.0 mg	10 mL

the children. Children over 12 years of age comprised 55% of the study population.

The French Transparency Commission issued a favourable opinion on the reimbursement of rivaroxaban tablets and granules for the treatment and prevention of VTE recurrences in children after at least 5 days of prior parenteral anticoagulation [19]. A favourable opinion concerning the authorisation of advanced access to rivaroxaban (XARELTO 1 mg/mL®) granules for oral suspension was issued on 23/09/2021 for the following indication: ''Treatment of venous thrombotic events and prevention of recurrences in the form of VTE, in neonates born at term, infants, young children, and children and adolescents under 18 years of age, after at least 5 days of initial parenteral anticoagulation''. With respect to newborns, the Marketing Authorisation is limited to neonates born at term, after at least 37 weeks of gestation, weighing at least 2.6 kg and having been fed for at least 10 days. The Commission recommends an initial in-hospital prescription of rivaroxaban in children, with specific therapeutic training conducted by a multidisciplinary team. Dispensing of the treatment to the patient is conditional on attestation of this training (Table 4).

Dabigatran: one phase III trial evaluated the use of dabigatran for the treatment of VTE in children from birth up to the age of 18 years. This study demonstrated the efficacy and good safety profile of dabigatran compared to those of heparins or VKA. A second phase III trial demonstrated the innocuity of dabigatran in the secondary prevention of VTE in paediatric patients [20]. Although dabigatran has been authorised for the treatment of childhood VTE elsewhere in Europe since January 2021, the French Health Authority has not yet issued an opinion. For this reason, in addition to the absence of a suitably adapted pharmaceutical formulation, we do not further consider dabigatran for the treatment of paediatric VTE.

Apixaban: a phase III trial, as well as a phase IV study, are currently ongoing to evaluate the safety and efficacy of apixaban in paediatric patients. The phase III trial is evaluating the effect of apixaban administration in comparison to no anticoagulant administration in the prevention of thrombosis in children presenting leukaemia or lymphoma. To participate in the trial, patients must be receiving chemotherapy, including asparaginase, and have undergone insertion of a central catheter. Patients weighing less than 35 kg will receive a fixed dose of apixaban based on their body weight twice a day for 28 days, while patients weighing more than 35 kg will receive 2.5 mg twice a day for 28 days. The primary efficacy endpoint is a composite of non-fatal deep-vein thrombosis (DVT) and pulmonary oedema (PE), thrombosis of the cerebral venous sinus and VTE-related death up to 1 month after the end of treatment. The phase IV trial is an open study, evaluating the safety and efficacy of apixaban in paediatric patients requiring anticoagulation for the treatment of VTE. Patients will receive either a standard-of-care anticoagulant, or apixaban at fixed doses based on body weight. Participants weighing 35 kg or more will receive 10 mg twice a day for 7 days, followed by 5 mg twice a day. Participants weighing less than 35 kg will receive doses according to a staged posology. The phase IV study concerning the treatment of childhood VTE with apixaban is currently still in the recruitment phase [21].

Edoxaban: a phase III trial was recently completed and is awaiting publication [22]. This trial assessed the pharmacokinetics and pharmacodynamics of edoxaban and evaluated its efficacy and safety in comparison with standard care in paediatric patients presenting confirmed VTE. Patients aged between 12 and 18 years received 15 mg or 30 mg tablets of edoxaban, those aged under 12 years received doses according to their body weight in the form of a suspension.

The DANNOAC-VTE trial (Danish Non-vitamin K Antagonist Oral Anticoagulation Study) is a recently initiated phase IV cluster-randomised study comparing the safety and efficacy of edoxaban, apixaban, rivaroxaban and dabigatran for the treatment of patients presenting VTE [23].

Agents reversing the action of apixaban, rivaroxaban and dabigatran have now been approved by the FDA. However, owing to the lack of data concerning their efficacy and security in the paediatric context, these agents have not yet been approved for use in children.

Thrombolysis

Thrombolysis is initiated only in the event of a life-threatening risk (serious pulmonary embolism).

Table 5 Summary of recommendations relating to treatment duration [3,14].

ACCP (2012)[a]		
Children with VTE secondary to a clinical risk factor in whom the risk factor has resolved	3 months	2C
Children with VTE secondary to an ongoing (but potentially reversible) clinical risk factor	Minimum of 3 months; continue anticoagulation beyond 3 months at either therapeutic or prophylactic doses until the risk factor is resolved	2C
Children with recurrent secondary VTE due to an existing reversible risk factor	Continue until the risk factor is resolved (minimum of 3 months)	2C
ASH (2018)		
Provoked DVT or PE	$\leq$ 3 months; longer anticoagulation may be considered in patients showing persistence of the causative risk factor	Conditional recommendation; very low certainty of evidence
Unprovoked DVT or PE	6 to 12 months	Conditional recommendation; very low certainty of evidence

ACCP: American College of Chest Physicians; ASH: American Society of Hematology; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism.
[a] ACCP strength of recommendations: 1A = strong recommendation, high-quality evidence; 1B = strong recommendation, moderate-quality evidence; 2C = weak recommendation, low- or very-low-quality evidence.

Rivaroxaban is the only DOAC that can be currently recommended in France for children (born at term).

No antidote to rivaroxaban has yet been approved for use in children.

Duration of anticoagulant treatment

In 2012, the American College of Chest Physicians (ACCP) published a complete set of guidelines concerning the treatment and prevention of VTE [14]. Although these guidelines have been partially updated in recent years, the recommendations relating to paediatric and neonatal patients have not yet been revised. The American Society of Hematology (ASH) published updated recommendations concerning paediatric VTE in 2018 [3] (Table 5).

The recommendations relating to the duration of treatment for children with VTE have been extrapolated from data concerning VTE in adult populations, owing to the lack of available data from well-conducted clinical trials in the paediatric population. The Kids-DOTT trial, an international, open-label, controlled, blindly randomised study, recruited patients under 21 years of age presenting acute VTE associated with a provoking factor [24]. The most frequent VTE-provoking factor was the presence of a central venous catheter (in 52.5% of cases), followed by an infection (34%), or a trauma or surgical intervention during the 30 days preceding the thrombotic event (19.9%). The choice of anticoagulant was at the physician's discretion, but the dose of the anticoagulant selected was defined in accordance with the 2012 ACCP recommendations. The authors concluded that a 6-week duration of anticoagulant treatment was not inferior to a 3-month duration. The limitation of this study was the small number of patients presenting cancer or pulmonary embolism.

For thromboses associated with a temporary provoking factor, the suggested duration of treatment is 6 weeks for patients whose characteristics are consistent with the study inclusion criteria [24].

For unprovoked VTE, curative anticoagulation is recommended. A treatment duration of 3 to 12 months is suggested, depending on the extent of the thrombosis, its gravity, and the risk of bleeding. The precise duration of treatment should be defined after multidisciplinary discussion.

In the case of thrombosis associated with a central catheter, or a catheter inserted via the umbilical vein, removal of the catheter after 5 to 7 days of anticoagulation is suggested, rather than leaving the catheter in place [11], followed by anticoagulant treatment at curative doses for 6 weeks to 3 months. For patients at high risk of bleeding, clinical and echographic monitoring may be proposed. For children with cancer, a 3-month anticoagulant treatment is suggested, for as long as the provoking factor (e.g., asparaginase infusion) remains present.

For children experiencing an initial VTE in the context of deep-vein malformations, a limited anticoagulant treatment for 3 to 12 months is suggested. In the event of recurrence, a longer treatment may be considered.

For thromboses associated with a temporary provoking factor, the suggested duration of anticoagulant treatment is 6 weeks.

In the case of VTE onset in the absence of any provoking event, curative anticoagulation for 3 to 12 months is recommended, subject to multidisciplinary discussion.

In the case of thrombosis associated with a central catheter or a catheter inserted via the umbilical vein, withdrawal of the catheter after 5 to 7 days of anticoagulation is suggested, followed by anticoagulation at curative doses for 6 weeks to 3 months.

For children with a cancer, anticoagulation for 3 months is suggested, as long as the precipitating factor remains present.

For children experiencing a first VTE in the context of deep-vein malformations, anticoagulant treatment limited to 3 to 12 months is suggested. In the event of recurrence, a more prolonged treatment may be considered.

Conclusion

Venous thrombosis during childhood is considered as a rare disease, in most cases occurring in predisposing circumstances in sick children.

The duration of anticoagulant treatment should preferably be short, given the low risk of recurrence.

Rivaroxaban is a very attractive alternative to the usual treatment by LMWH or VKA.

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Sophie Blaise and Marjolaine Talbot declare that they have no competing interest.

Gabrielle Sarlon declares that she has conflicts of interest with BMS Pfizer.

Léo Pharma and Sanofi (conferences: invitations as auditor [travelling and accommodation expenses paid for by the company and expert on boards]).

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Sophie Blaise: investigation,validation, writing — original draft, review and editing.

Gabrielle Sarlon: investigation, validation and writing — original draft.

Marjolaine Talbot: writing and review.

Guillaume Mahe: conceptualization, methodology and review.

Alessandra Bura-Riviere: investigation,validation and writing — original draft.

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