

Minimizing perioperative blood loss and transfusions in children

[Réduire les pertes sanguines et les besoins transfusionnels en chirurgie pédiatrique]

Joanne Guay MD FRCPC,* Philippe de Moerloose MD,† Dominique Lasne MD‡

Purpose: To summarize the physiology and pathophysiology relevant to perioperative blood loss in children. Strategies to reduce blood losses are reviewed.

Methods: The literature was reviewed using the electronic library PUBMED and the Cochrane Database of Systematic Reviews. Relevant studies published in English or French with an English abstract are included. The following keywords were used: children, blood transfusion, surgical blood loss, erythropoietin, autologous blood, red blood cell saver, normovolemic hemodilution, desmopressin, aminocaproic acid, tranexamic acid, aprotinin, cardiac surgery, liver transplantation and scoliosis surgery.

Main findings: For patients with idiopathic scoliosis, predonation with or without the addition of erythropoietin is a safe and effective way to avoid the use of allogenic blood products. For open heart procedures: whole blood of less than 48 hr is helpful for children of less than two years of age undergoing complex procedures; tranexamic acid may be helpful for cyanotic heart disease and, to a lesser degree, for reoperations; while anti-kallikrein blood levels of aprotinin may both reduce the need for allogenic blood transfusions and improve postoperative oxygenation in infants.

Conclusion: Reducing perioperative allogenic blood transfusions is possible in pediatric patients provided that prophylactic measures are adapted to age, disease and type of surgery.

Objectif : Revoir la littérature pertinente à la prise en charge des pertes sanguines péri-opératoires de l'enfant ainsi que les stratégies d'épargne sanguine.

Méthode : La littérature a été revue à l'aide de la banque de données électronique PUBMED et du Cochrane Database of Systematic Reviews. Les études pertinentes publiées en langue française ou anglaise avec résumé en langue anglaise ont été revues. Les mots-clés suivants ont été utilisés : enfant, transfusion sanguine, pertes sanguines chirurgicales, érythropoïétine, transfu-

sion autologue préprogrammée, récupérateur de globules rouges, hémodilution isovolémique, desmopressine, acide aminocaproïque, acide tranexamique, aprotinine, chirurgie cardiaque, transplantation hépatique et arthrodeèse vertébrale.

Constatations principales : Pour les scolioses idiopathiques, la transfusion autologue programmée avec ou sans l'ajout d'érythropoïétine réduit l'administration de sang homologue. Pour les chirurgies à cœur ouvert, le sang complet de moins de 48 h est utile pour les corrections de cardiopathies complexes avant l'âge de deux ans, l'acide tranexamique est utile pour les corrections de cardiopathies cyanogènes et à un degré moindre pour les réinterventions alors que l'aprotinine à dose anti-kallikréine diminue les besoins transfusionnels et améliore l'oxygénation postopératoire en dessous de l'âge de un an.

Conclusion : Il est possible de réduire les transfusions allogènes chez l'enfant si des mesures adaptées à l'âge, à la pathologie et au type de chirurgie sont appliquées.

IN normal children perioperative blood loss leading to administration of allogenic transfusion may be encountered if: the surgical site does not allow easy access to surgical hemostasis, the surgery is performed on highly vascularized tissues that are not easily sutured or cauterized (for example bone elements such as in spinal fusion or correction of craniosynostosis) or the surgery itself induces various disturbances of hemostasis (dilution of factors and induction of fibrinolysis as in cardiac surgery with the use of extracorporeal bypass). The pathology justifying the surgical procedure may also induce various coagulation and/or hemostatic abnormalities. Children suffering from congenital cardiac or liver dis-

From Departments of Anesthesiology, Maisonneuve-Rosemont Hospital,* University of Montreal, Montreal, Quebec, Canada; University Hospital of Geneva,† Geneva, Switzerland; and the Laboratoire d'hématologie,‡ Hôpital Necker, Paris, France.

Address correspondence to: Dr. Joanne Guay, Department of Anesthesiology, Maisonneuve-Rosemont Hospital, 5415 L'Assomption Blvd, Montreal, Quebec H1T 2M4, Canada. Phone: 514-252-3426; Fax: 514-252-3542; E-mail: joanne.guay@umontreal.ca

ease may have thrombocytopenia, abnormal platelet function (congenital heart disease) and/or inadequate amounts of various coagulation factors.¹ Perioperative management of children with congenital coagulation and hemostatic diseases will not be discussed in this review.

Developmental aspects of hemostasis

An excellent summary of the developmental physiology of coagulation, based mainly on the extensive work of Maureen Andrew, may be found in a recent review by Kuhle *et al.* and is summarized in Table I.² Since maternal coagulation factors do not cross the placental barrier, blood levels measured at birth are the result of fetal synthesis that starts around the fifth week of gestation. Fetal blood becomes clottable around 11 weeks of gestation. Except fetal fibrinogen which has an increased content of sialic acid, all coagulation and inhibitor factors are qualitatively normal at birth, and differ from adults in their quantity only. Factor VIII would be the only factor present in normal quantity at birth. In neonates and up to six months of age where they reach approximately 80% of adult values, plasma levels of vitamin K-dependent factors (II, VII, IX and X) are reduced, but the prothrombin time (PT) remains within normal limits. The activated partial PT (aPTT) is slightly prolonged up to three months of age as a result of decreased blood levels of contact factors (XII, prekallikrein and high molecular-weight

kininogens). A decrease in platelet function during the first years of life has also been shown.³ Clinical implications of the prolonged aPTT observed up to three months of age and of decreased platelet function throughout childhood are unclear, since measurement of whole blood coagulation shows a relative hypercoagulable state as demonstrated by a decreased reaction-time with the thromboelastograph in infants (under one year of age).⁴ Moreover, the bleeding time is shorter in newborns. This might be due to higher levels of von Willebrand factor and increased hematocrit. Finally, except for cardiac surgery with the use of extracorporeal bypass where higher blood losses in infants have been clearly demonstrated, neonates usually do not demonstrate excessive bleeding during surgery.⁵

In vitro studies report both increased and decreased heparin sensitivity for neonates. These apparently contradictory results can be explained by an increase in the antithrombin to thrombin ratio (1.5:1 in neonates compared to an arbitrary reference value of 1:1 for adults). Thus, if the test used to measure anticoagulation is based on the generation of thrombin, results will be compatible with increased heparin sensitivity.^{1,6} Though an increased sensitivity of newborn and children plasma to heparinoids has been described, children under one year of age will require higher heparin doses per kilogram of body weight than adults.^{7,8}

TABLE I Reference values for neonates, infants, children and adults: laboratory tests and thromboelastograph data

Laboratory test	Neonates		Infants	Children		Pre- and adolescents	Adults
	1 day	30 days	6 months	1 to 5 yr	6 to 10 yr	10 to 16 yr	
Prothrombin time (sec)	13.0 (10.1–15.9)	11.8 (10.0–14.3)	12.3 (10.7–13.9)	11.0 (10.6–11.4)	11.1 (10.1–12.1)	11.2 (10.2–12.0)	12.0 (11.0–14.0)
International normalized ratio	1.0 (0.53–1.62)	0.79 (0.53–1.26)	0.88 (0.61–1.17)	1.00 (0.96–1.04)	1.01 (0.91–1.11)	1.02 (0.93–1.10)	1.10 (1.00–1.30)
Activated partial thromboplastin time (sec)	42.9 (3.13–54.9)	40.4 (32.0–55.2)	35.5 (28.1–42.9)	30.0 (24.0–36.0)	31.0 (26.0–36.0)	32.0 (26.0–37.0)	33.0 (27.0–40.0)
Thrombin clotting time (sec)	23.5 (19.0–28.3)	24.3 (19.4–29.2)	25.5 (19.8–31.2)				
Bleeding time (min)				6.0 (2.50–10.0)	7.0 (2.50–13.0)	5.0 (3.00–8.00)	4.00 (1.00–7.00)
<i>Thromboelastograph</i>							
Reaction time (min)	12.8 ± 3.7	13.0 ± 3.3	12.0 ± 4.0	13.5 ± 3.1	14.0 ± 3.4		16.1 ± 3.1
K (min)	8.3 ± 2.5	6.2 ± 1.5	6.6 ± 1.8	7.9 ± 1.7	8.5 ± 1.9		9.2 ± 2.4
α angle (°)	35.5 ± 10.1	45.8 ± 7.4	42.6 ± 8.9	36.9 ± 6.7	35.3 ± 7.6		30.1 ± 6.7
Maximal amplitude (mm)	58.6 ± 7.3	65.4 ± 5.2	61.3 ± 6.6	58.6 ± 4.9	58.3 ± 4.5		51.6 ± 5.8
Amplitude at 60 min after maximal amplitude (mm)	52.9 ± 7.8	58.8 ± 6.1	55.0 ± 6.6	52.1 ± 5.6	51.6 ± 5.3		46.6 ± 6.7

Laboratory values are expressed as mean and range to encompass 95% of the population and thromboelastograph values as mean ± SD. From Kuhle *et al.* *Sem Thromb Hemost* 2003; 29: 329–37 and Miller *et al.* *Anesth Analg* 1997; 84: 745–8.

Preoperative laboratory investigation

The Canadian Anesthesiologists' Society proposes that before any surgery: "Laboratory investigations indicated by the history and physical examination should be carried out. These should take into consideration the physical condition of the patient and the proposed operation". When the patient's personal or familial history discloses possible congenital or acquired diseases of hemostasis or the proposed surgery generally implies major blood loss, coagulation screening is indicated. Recommendations, however, are not as clear for healthy children undergoing a surgery with a low or moderate risk of intra- or postoperative bleeding. Though many valuable studies have tried to evaluate the cost/benefit ratio of routine coagulation screening tests before adeno-tonsillectomy, the question remains unresolved. Although screening assays have been abandoned by many specialized centres, coagulation tests are still ordered by some physicians before an adeno or tonsillectomy (45–81%).^{9,10} Post-tonsillectomy hemorrhage occurs in 1.6 to 3.5% of the patients and is less frequent in younger children (under three years of age) despite the risk of undiagnosed hematologic disease in those children.^{11,12} On the other hand, history alone may fail to detect patients with congenital or acquired bleeding disorders, even those with diseases as severe as hemophilia type A.¹³ In predicting adeno-tonsillectomy perioperative bleeding, history coupled with routine classical laboratory screening tests (including PT, aPTT, platelets count) has both a low sensitivity and a very low post-test probability due to the low prevalence of bleeding. When routine coagulation tests are performed, abnormal tests are found in approximately 3% of children but diseases susceptible to induce abnormal perioperative bleeding occur in only 0.5% of the children, von Willebrand's disease and factor XI deficiency being by far the two most common diseases encountered.^{14,15} The prevalence of von Willebrand's disease in the surgical population is estimated at 0.6%.¹⁶ Thus, if the clinician chooses to evaluate the coagulation status of all children undergoing adeno-tonsillectomy, aPTT measurement and a platelet function test would probably be the most useful. For evaluation of platelet function, bleeding time was often performed in this setting. However this test (which can leave long term scars) can be advantageously replaced by newer on-site monitoring devices such as the PFA-100 which has been shown to offer a higher sensitivity to detect von Willebrand's disease: for example, in one study, 100 and 87% for epinephrine and adenosine diphosphate cartridge, respectively, compared to only 37% for the bleeding time.¹⁷ For PT or international normalized

ratio measurements in the pediatric population, and for international normalized ratio values ranging from 1.05 to 5.25, the near patient instrument with the least bias relative to the classical laboratory test (CA-1000) is the RapidpointCoag® ($r^2 = 0.923$), the correlations (r^2) of the CoaguCheck®, Hemochron Jr®, and ProTime® being 0.877, 0.834, and 0.885, respectively.¹⁸ Bilirubin levels up to 20 mg·dL⁻¹ (342 µmol·L⁻¹) do not interfere with any of these methods. For other types of surgery, preoperative coagulation tests have been reported to be useful in predicting the magnitude of blood losses in open heart, liver transplant and scoliosis surgery.^{19–21} Routine coagulation tests have also been recommended by some before any neuraxial blockade in children under one year of age, but the real benefit of this recommendation remain to be shown.²²

Patient and surgical risk factors known to increase perioperative blood loss

A good knowledge of the surgical technique itself will help in predicting blood loss, determine the extent of prophylactic measures needed to avoid allogenic blood transfusions, and prepare for blood loss replacement. For scoliosis surgery, the number of fused vertebrae and the presence or absence of an underlying disease such as neuromuscular dystrophies are probably the most important factors that determine the magnitude of blood loss.^{23,24} For repair of craniosynostosis, the type of skull deformation and surgical procedure determine the extent of intraoperative bleeding.²⁵ For orthognatic surgery, double-jaw procedures result in more blood loss than single-jaw procedures, boys have a higher average blood loss than girls, but average blood loss is not significantly affected by patients' age.²⁶ For pediatric open heart surgery, risk factors clearly associated with increased blood loss include: age less than one month, body weight under 8 kg, complexity of the procedure (arterial switches for transposition of the great vessels, Fontan procedures, Glenn shunts and truncus arteriosus repairs), duration of cardiopulmonary bypass, resternotomy, and low platelet count during cardiopulmonary bypass.^{1,5,27–30} For pediatric liver transplants, apart from retransplantation, factors that have been associated with increased intraoperative blood losses include: hypoplastic portal vein, use of a reduced-size liver graft, requirement of in-hospital supportive care, intra-abdominal malformations and signs of severe liver failure (encephalopathy, ascites, prolonged PT).^{20,31–33} Children younger than two years, and particularly those under one year of age experience higher blood loss.^{34,35} Transplantation of a reduced (fraction of an adult human organ) liver not

TABLE II Reducing allogenic blood transfusions in children undergoing non-cardiac surgery

	<i>Craniostenosis repair</i>	<i>Spinal fusion</i>	<i>Liver transplantation</i>	<i>Study protocol</i>	<i>Authors</i>
Erythropoietin	↓ABT	↓ABT		Prospective randomized Retrospective, more effective in idiopathic scoliosis	Fearon <i>et al.</i> ³⁷ Vitale <i>et al.</i> ³⁸
Red blood cell predonation		↓ABT		Retrospective, more effective in idiopathic scoliosis	Murray <i>et al.</i> ³⁹
Acute intraoperative normovolemic hemodilution	→ABT			Prospective randomized	Hans <i>et al.</i> ⁴⁰
Intraoperative autotransfusion		↓aBT; →ABT		Retrospective, case control	Copley <i>et al.</i> ⁴¹
Desmopressin		↓aBT; →ABT		Retrospective, idiopathic scoliosis	Siller <i>et al.</i> ⁴²
		→ABT or aBT		Prospective, randomized, idiopathic scoliosis	Guay <i>et al.</i> ⁴³
		→ABT		Prospective, randomized, neuromuscular disease	Theroux <i>et al.</i> ⁴⁴
		→BL		Prospective, randomized, neuromuscular disease	Letts <i>et al.</i> ⁴⁵
Aminocaproic acid		↓ABT		Prospective, non-randomized, idiopathic scoliosis	Florentino-Pineda <i>et al.</i> ⁴⁶
Tranexamic acid		↓BL for secondary scoliosis, →aBT*		Prospective, randomized, mixed population	Neilipovitz <i>et al.</i> , ⁴⁷ Sethna ⁴⁸
Aprotinin		↓BL and number of transfused unit		Prospective, mixed population	Cole ⁴⁹
		→BL		Prospective, randomized idiopathic scoliosis	Khoshhal <i>et al.</i> ⁵⁰
			→ABT	Retrospective	Rentoul <i>et al.</i> ⁵¹

ABT = allogenic blood transfusion; aBT = autologous blood transfusion; BL = blood loss. ↓ = decrease or → = no change in the percentage of patients with ABT or aBT; or BL. *For reference 48, the volume of transfused blood was decreased, but not the number of patients transfused.

only increases intra- and postoperative blood loss, but has been associated with an increase in the percentage of patients undergoing reoperation for continued blood loss, from 9.6 to 19.2%.³⁶

Reducing allogenic blood transfusions

As in adults, various strategies have been used to reduce allogenic blood transfusion in children.³⁷⁻⁵¹ Of all the types of surgeries, spinal fusion and cardiac operations have been the most extensively studied (Tables II and III). For patients with idiopathic scoliosis, predonation with or without the addition of erythropoietin is probably the safest and the most effective way to avoid the use of allogenic blood products. When an adequate amount of predonated blood is available, acute normovolemic hemodilution, intraoperative blood salvage and retransfusion, as well as antifibrinolytics agents offer little to further reduce allogenic blood transfusion, with the possible exception of patients with predicted blood losses over

2000 mL or small body weight.⁵² Desmopressin has been proven ineffective for idiopathic as well as neuromuscular disease induced-scoliosis.^{43,44} The safety of retransfusing shed wound blood has not been well established. This practice carries a definite risk of bacterial contamination and, for scoliosis or open heart surgery,⁵³ cannot be recommended. Recombinant factor VIIa may be another therapeutic tool to reduce perioperative allogenic blood transfusion, but has not been studied systematically in children so far. This drug has, however, been reported to benefit two patients with neuromuscular disease induced-scoliosis with severe postoperative dilutional coagulopathy unresponsive to plasma administration.⁵⁴

Blood conservation strategies studied for open heart surgery are summarized in Table III.^{28,29,55-63} The population studied should be taken into account to interpret published results: age, complexity of surgery, cyanotic/acyanotic disease and reoperations.^{1,61} When available, whole blood of less than 48 hr is helpful

TABLE III Reducing allogenic blood transfusion in pediatric open heart surgery

	<i>Acyanotic</i>	<i>Cyanotic</i>	<i>Mixed population</i>	<i>Complex surgery</i>	<i>Reoperation</i>	<i>Study protocol</i>	<i>Authors</i>
Erythropoietin			↓ABT*			Compared to historical controls	Sonzogni <i>et al.</i> ⁵⁵
Desmopressin			→BL			Prospective randomized	Seear <i>et al.</i> ²⁹
				→BL		Prospective randomized	Reynolds <i>et al.</i> ⁵⁶
Aminocaproic acid	→BL	↓BL				Prospective randomized	McClure <i>et al.</i> ⁵⁷
Tranexamic acid		↓BL, ABT in mL·kg ⁻¹				Prospective randomized	Zonis <i>et al.</i> ⁵⁸
				↓BL and number of donor unit exposure		Prospective randomized	Reid <i>et al.</i> ⁵⁹
Aprotinin					↓BL and number of donor unit exposure	Prospective randomized	D'Errico <i>et al.</i> ⁶⁰
Autologous platelet concentrates	↓BL					Prospective non-randomized	Hiramatsu <i>et al.</i> ⁶²
Fresh frozen plasma in the prime		↓BL	↑Number of unit transfused	↓BL		Prospective randomized with post hoc analysis	Oliver <i>et al.</i> ⁶³
Whole blood of less than 48 hr				↓BL†		Prospective non-randomized	Manno <i>et al.</i> ²⁸

ABT = allogenic blood transfusion; BL = blood loss; ↓ = decrease or → = no change in the percentage of patients with ABT or in BL. * Plus two predonated units of 6 mL·kg⁻¹. †Less than two years of age.

for children less than two years of age undergoing complex procedures.²⁸ The efficacy of fresh whole blood might be attributed to better platelet preservation. Platelet predonation and reinfusion is an elegant technique to decrease bypass induced-platelet activation.^{62,64} Erythropoietin with red blood cell predonation could be helpful in acyanotic heart disease.⁵⁵ The addition of fresh frozen plasma to the pump prime could possibly help children with cyanotic heart disease and those with complex surgery, but the risk of transmitting infectious diseases must be weighed against the potential benefits. Among the antifibrinolytic agents, tranexamic acid might be the most appropriate, at least for cyanotic heart disease and, to a lesser degree, for reoperations. Apart from its lower cost, since it is entirely synthetic, risks of disease transmission should be inexistent. Moreover, risks of inducing an anaphylactic reaction after reexposure are much lower than those reported for aprotinin. One study, however, suggests that, in infants (less than 10 kg of body weight), if anti-kallikrein blood levels are maintained throughout the surgery, aprotinin might not only reduce the need for allogenic blood transfusions, but might also improve postoperative oxygenation.⁶⁵

Administration of blood products

Blood volume can be estimated from the patient's body weight and age (Table IV). Maximal blood losses allowed before administration of red blood cells and plasma will vary according to age and associated diseases. There are actually very few pediatric data which could help determine the minimal acceptable hemoglobin concentration in children. In one study of more than 200 pediatric cardiopulmonary arrests, there was no long term survival in children with a pre-arrest hemoglobin concentration less than 57 g·L⁻¹.⁶⁶ Some authors believe that infants less than four months old should be considered as a different population, while others have fixed a limit at one year of age.^{67,68} For children over six to 12 months of age without cardiac or respiratory disease, a minimal hemoglobin concentration of 70 g·L⁻¹, as recommended for adults, is probably acceptable.⁶⁹ For younger patients, it is probably advisable to maintain a minimal hemoglobin concentration of 80 to 90 g·L⁻¹,⁶⁸ although clinical data to support such a recommendation are lacking. Assuming that blood volume remains normal, the maximal amount of blood loss that can be tolerated before administration of red blood cells can be calculated with the following formula:

$$\text{MBL (mL)} = [(\text{Hcti} - \text{Hctf})/\text{Hctm}] \times \text{EBV}$$

Where:

MBL: maximal blood loss allowed before administration of red blood cells

Hcti: initial hematocrit level

Hctf: minimal hematocrit level that will be tolerated according to age and underlying diseases

Hctm: mean hematocrit level defined as $(\text{Hctf} + \text{Hcti})/2$

EBV: estimated blood volume (Table IV)

Irradiated blood is recommended for intrauterine red blood cell transfusions to the fetus, selected immunocompromised infants, newborns infants receiving blood from a relative, and infants who have previously received an *in utero* transfusion.⁷⁰ Most guidelines also recommend the provision of cytomegalovirus-negative blood components for low birth weight infants.⁷⁰

For children over six months of age, criteria for administration of fresh frozen plasma and platelet concentrates are the same as for adult patients. When the extent of blood loss approaches one blood volume, PT, aPTT and platelet count should be determined. With active bleeding and a PT and/or aPTT longer than one and a half times normal values, 15 to 20 mL·kg⁻¹ of fresh frozen plasma may be administered. For infants less than six months of age, many clinicians will start the administration of fresh frozen plasma with blood losses between 20 to 50% of the estimated blood volume as blood levels of coagulation factors are lower in this age group, and the administration of crystalloids as the sole replacement therapy for blood loss often leads to hemodynamic instability. Administration of fresh frozen plasma may also be indicated earlier for children with certain underlying diseases, such as hepatic insufficiency (when presenting for liver transplantation) or congenital cardiopathy.^{71,72} Though the literature on this subject is virtually non-existent, administration of colloid solutions in children is part of the standard practice of many centers. At least one study demonstrated that, in children, hemostatic variables will not be affected by the administration of colloid solutions (even after cardiopulmonary bypass) until a volume greater than 20 mL·kg⁻¹ is administered.⁷³ The administration of 0.1 unit of platelets per kilogram of body weight should increase the platelet count by 7 to 11 G·L⁻¹. The minimal acceptable platelet count will vary between 50 and 100 G·L⁻¹ depending on the type of surgery and the presence of other hemostatic diseases and/or coagulopathies. Administration of 0.5 U·kg⁻¹ of cryoprecipitate (when available) may be indicated for

TABLE IV Normal hemoglobin values and blood volumes for age

	Hemoglobin (g·L ⁻¹)	Estimated blood volume (mL·kg ⁻¹)
Premature	180–220	90–100
Newborn	100–110	80–90
Six months to two years	120–130	80
> two years	120–130	70

factor VIII levels lower than 0.5 U·mL⁻¹ or fibrinogen levels lower than 1 g·L⁻¹ and to restore blood factor levels in infants for whom the administration of large amounts of fluids may pose a problem. For example, in infants less than 8 kg of body weight who have undergone open heart surgery, coagulation factor levels are better restored by cryoprecipitates than by fresh frozen plasma, which may induce further dilution of coagulation factors.²⁷ If cryoprecipitates are unavailable, specific factor concentrates may be used.

Warming of blood products is mandatory in children who may be particularly sensitive to hypothermia. Citrate intoxication with hypocalcemia is possible if the speed of administration exceeds 3 mL·kg⁻¹·min⁻¹ for red blood cells and 1.5 to 2.0 mL·kg⁻¹·min⁻¹ for fresh frozen plasma. Hyperkalemia has also been reported with rapid red blood cell administration in children, especially if volemia has not been properly restored first.⁷⁴

Conclusion

The management of perioperative blood loss in children requires good clinical knowledge of the developmental physiology and of the pathophysiology of diseases affecting children coming to surgery. Reducing allogenic blood transfusions is possible in this age group, provided that prophylactic measures are adapted to age, disease and type of surgery.

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