Hemostatic Agents Used to Stop Bleeding

34

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Tranexamic Acid

Brand Names (USA): Lysteda™, Cyklokapron™
Description: Tranexamic acid is a synthetic amino acid that is classified as antifibrinolytic. It is a competitive inhibitor of plasminogen activation, which becomes a noncompetitive inhibitor at higher concentrations. Tranexamic acid displaces plasminogen from fibrin and results in the inhibition of fibrinolysis. Tranexamic acid is approximately ten times more potent than aminocaproic acid, and its elimination half-life is 2–11 h [1, 2]. Tranexamic acid is available in an intravenous solution and an oral tablet. In addition, an oral solution may be compounded. If 10 mL of the compounded oral 5 % solution is swallowed, this provides 500 mg of tranexamic acid orally [3]. However, this oral solution is mostly studied for topical use.

Adult Use: Tranexamic acid can be used for menorrhagia [2], blood loss reduction during elective cesarean section [4], blood loss reduction during hip fracture surgery [5], blood loss reduction in orthognathic surgery [6], blood loss reduction in dental procedure patients on oral anticoagulant therapy [7], prevention of perioperative bleeding associated with cardiac and spinal surgery [8–11], blood loss reduction during total hip and total knee replacement surgery [12–18], and trauma-associated hemorrhage [19].

Pediatric Use: In the pediatric setting, tranexamic acid can be used for the prevention of bleeding associated with extracorporeal membrane oxygenation (ECMO) during surgery for congenital diaphragmatic hernia (CDH) repair [20, 21], prevention of perioperative bleeding associated with cardiac surgery [22–24], menorrhagia [2], blood loss reduction in hemophilia patients undergoing tooth extraction [25], treatment of hemoptysis in cystic fibrosis patients [26–28], and prevention of perioperative bleeding associated with spinal surgery and craniosynostosis surgery [29–32].

Adverse Effects and Monitoring Parameters: Orally administered tranexamic acid can cause gastrointestinal upset, headache, abdominal pain, muscle pain, and thrombosis (Table 34.1). Visual defects may occur; thus, patients should undergo routine ophthalmologist examinations. Intravenous tranexamic acid can also cause hypotension with rapid administration [33]. The dose and frequency of tranexamic acid should be adjusted in patients with renal dysfunction (see Table 34.2). Importantly, tranexamic acid should not be used when there is evidence of active intravascular thrombosis [1, 2]. Caution is advised if antifibrinolytics are used together with prothrombin complex concentrates (PCC) or activated prothrombin complex concentrates (APCC) because of the risk of thrombosis. If treatment with both agents is deemed necessary, it is recommended to wait 4–6 h after the last dose of PCC or APCC before administering antifibrinolytics [34].

Aminocaproic Acid

Brand Name (USA): Amicar™
Description: Aminocaproic acid is an antifibrinolytic that binds competitively to plasminogen, which reduces the conversion of plasminogen to plasmin, resulting in the inhibition of fibrin degradation. The main difference between aminocaproic acid and tranexamic acid is that tranexamic binds more strongly to plasminogen; thus, aminocaproic acid is less potent than tranexamic acid. Aminocaproic acid has an elimination half-life of 2 h and may accumulate in patients with renal dys-

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Table 34.1 Tranexamic acid dosing

Indication	Dose and frequency	Duration
Menorrhagia	1300 mg PO TID	Up to 5 days/month during menstruation
Blood loss reduction during elective cesarean section	1000 mg IV at least 10 min prior to incision	
Blood loss reduction during hip fracture surgery	15 mg/kg IV at time of skin incision followed by 15 mg/kg IV 3 h later	
Blood reduction during orthognathic surgery	20 mg/kg IV prior to incision	
Prevention of dental procedure bleeding in patients on oral anticoagulant therapy	Hold 10 mL of 4.8 % solution in mouth and rinse for 2 min	Repeat 4 times daily for 2 days after procedure. *Patient shouldn't eat or drink for 1 h after using oral rinse*
Prevention of perioperative bleeding associated with cardiac surgery	• 30 mg/kg IV prior to incision, followed by 16 mg/kg/h IV until sternal closure • 10 mg/kg IV prior to incision followed by 2 mg/kg/h IV continued for 2 h after surgery • 10–15 mg/kg IV followed by 1–1.5 mg/kg/h IV	
Prevention of perioperative bleeding associated with spinal surgery	• 2000 mg IV prior to incision followed by 100 mg/h IV during surgery and for 5 h postoperatively • 10 mg/kg IV prior to incision followed by 1 mg/kg/h IV for the remainder of the surgery; discontinue at time of wound closure	
Blood loss reduction during total hip replacement surgery	• 10–15 mg/kg (or 1000 mg) IV immediately before the operation or 15 min before skin incision • The preoperative dose may be followed by 10 mg/kg IV administered 3–12 h after the operation • Postoperative doses ranged from a 10 mg/kg IV bolus (or 1000 mg) to a 1 mg/kg/h IV infusion over 10 h	
Blood loss reduction in total knee replacement surgery	10 mg/kg (or 1000 mg) IV approximately 10 min before deflation of the first tourniquet with a second dose (10 mg/kg) 3 h after the first dose	
Trauma-associated hemorrhage	1000 mg IV followed by 1000 mg IV over the next 8 h	
Prevention of bleeding associated with ECMO during surgery for CDH	4 mg/kg IV before repair, followed by 1 mg/kg/h IV for 24 h	
Prevention of perioperative bleeding associated with cardiac surgery in neonates	100 mg/kg IV Prime the bypass circuit with 100 mg/kg IV followed by 10 mg/kg/h IV infusion	
Prevention of bleeding associated with cardiac surgery in children	6.4 mg/kg IV followed by 2–3 mg/kg/h IV infusion	
Prevention of perioperative bleeding associated with spinal surgery in children	20 mg/kg IV and 10 mg/kg/h IV infusion OR 10 mg/kg IV and 1 mg/kg/h IV infusion	
Prevention of perioperative bleeding associated with craniosynostosis surgery in children	• 50 mg/kg IV prior to incision, followed by 5 mg/kg/h IV infusion until skin closure OR • 15 mg/kg IV prior to incision, followed by 10 mg/kg/h IV infusion until skin closure	
Treatment of hemoptysis in cystic fibrosis patients	• 60 mg/kg/day IV every 6 h × 1 day, then switch to 500 mg PO QID (90 mg/kg/day), then 500 mg PO TID × 4 years with no toxicity • 500 mg PO TID × 5 months • 1000 mg PO TID chronic treatment	
Usual dosing: 15–25 mg/kg PO every 8 h or 10 mg/kg IV every 8 h		

Adapted from references [1–32]

Table 34.2 Tranexamic acid dosing in renal impairment

Indication	Serum creatinine	Dose and frequency
Menorrhagia	>1.4–2.8 mg/dL	1300 mg PO BID for up to 5 days
	2.9–5.7 mg/dL	1300 mg PO daily for up to 5 days
	>5.7 mg/dL	650 mg PO daily for up to 5 days
Blood loss reduction in adult cardiac surgery patients	>1.4–2.8 mg/dL	1300 mg twice daily (2600 mg daily) for up to 5 days
	2.9–5.7 mg/dL	1300 mg once daily for up to 5 days
	>5.7 mg/dL	650 mg once daily for up to 5 days
Blood loss reduction in pediatric and adult hemophilia patients undergoing tooth extraction	1.36–2.83 mg/dL	10 mg/kg/dose IV BID
	>2.83–5.66 mg/dL	10 mg/kg/dose IV once daily
	>5.66 mg/dL	• 10 mg/kg/dose IV every 48 h • 5 mg/kg/dose IV once daily

Adapted from references [1, 24, 33]

Table 34.3 Aminocaproic acid dosing

Indication	Dose and frequency	Duration
Acute bleeding	4–5 g PO/IV during the first hour, followed by 1 g/h for 8 h (or 1.25 g/h using oral solution) or until bleeding controlled (max daily dose: 30 g)	
Control of bleeding with severe thrombocytopenia	100 mg/kg (max dose: 5 g) IV over 30–60 min, followed by 1–4 g IV/PO every 4–8 h or 1 g/h (max daily dose: 24 g)	
Control of oral bleeding in congenital and acquired coagulation disorder	50–60 mg/kg PO every 4 h	
Prevention of dental procedure bleeding in patients on oral anticoagulant therapy	Oral rinse: Hold 4 g/10 mL in mouth for 2 min then spit out	Repeat every 6 h for 2 days after procedure
Prevention of perioperative bleeding associated with cardiac surgery	• 10 g IV followed by 2 g/h during surgery; no medication added to the bypass circuit • 10 g IV prior to skin incision, followed by 10 g after heparin administration then 10 g at discontinuation of cardiopulmonary bypass	
Prevention of perioperative bleeding associated with cardiac surgery in pediatric patients	100 mg/kg IV after induction and prior to incision,100 mg/kg during cardiopulmonary bypass, and100 mg/kg after heparin reversal	
Prevention of bleeding associated with ECMO in pediatric patients	100 mg/kg IV prior to or immediately after cannulation, followed by 25–30 mg/kg/h for up to 72 h	
Prevention of perioperative bleeding associated with spinal surgery pediatric patients	100 mg/kg IV after induction, followed by 10 mg/kg/h for the remainder of the surgery; discontinue at time of wound closure	
Usual dosing: 60–100 mg/kg PO every 6 h (up to 24 g/day in adults)		

Adapted from references [35–47]

function. Thus, a reduced dose may be necessary in anephric patients or those with renal dysfunction. Aminocaproic acid is available as an intravenous solution, oral solution, and oral tablet [35, 36].

Adult Use: Aminocaproic acid can be used to enhance hemostasis when fibrinolysis contributes to bleeding [35], control of acute bleeding [35], control of bleeding with severe thrombocytopenia [37, 38], control of bleeding in congenital and acquired coagulation disorder [39], blood loss reduction in patients on oral anticoagulant therapy undergoing dental procedures [40], and prevention of perioperative bleeding associated with cardiac surgery [41, 42].

Pediatric Use: Aminocaproic acid can be used in children for the prevention of perioperative bleeding associated with cardiac and spinal surgery [42–44] and prevention of bleeding associated with ECMO [45–47].

Adverse Effects and Monitoring Parameters: The most common adverse effect of aminocaproic acid is gastrointestinal upset (Table 34.3). Other adverse effects include thrombosis and an increase in blood urea nitrogen (BUN) and skeletal muscle weakness. Aminocaproic acid can also cause skeletal muscle weakness; therefore, creatine phosphokinase (CPK) should be monitored, and treatment should be discontinued with a significant rise in CPK. Other monitoring parameters include fibrinogen, BUN, and creatinine. Importantly, aminocaproic acid should not be used when there is evidence of active intravascular thrombosis [35].

Fibrinogen Concentrate (Human)

Brand Name (USA): RiaSTAP™

Description: Fibrinogen concentrate (coagulation factor I) is generated from pooled human plasma and is a physiological substrate of thrombin, factor XIIIa, and plasmin. Soluble fibrinogen is converted to insoluble fibrin. Fibrin is stabilized by factor XIIIa, which induces cross-linking of fibrin polymers to provide strength and stability to the blood clot. The cross-linked fibrin is the end result of the coagulation cascade. Human fibrinogen concentration has a fairly long elimination half-life of 61–97 h; however, this half-life may be decreased in children and adolescents. Fibrinogen concentrate is available as intravenous powder, for reconstitution [48].

Adult Use: Fibrinogen concentrate can be used in the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia) [48], supportive therapy in trauma patients who are bleeding [49–53], blood loss reduction in cardiovascular surgery [49, 54, 55], blood loss reduction in postpartum hemorrhage [56], and improvement in clot firmness after orthopedic surgery [57].

Pediatric Use: Fibrinogen concentrate can be used in children for the treatment of congenital fibrinogen deficiency [58, 59] and reduction of blood loss after surgical craniosynostosis repair [60].

Adverse Effects and Monitoring Parameters: Fibrinogen concentrate may cause hypersensitivity reactions, thrombosis,

Table 34.4 Fibrinogen concentrate dosing

Indication	Dose, frequency, and duration
Congenital fibrinogen deficiency	[Target level (mg/dL) - measured level (mg/dL)] divided by 1.7 (mg/dL per mg/kg body weight) = mg/kg dose
	When baseline fibrinogen is unknown: 70 mg/kg IV
Traumatic bleeding	25–50 mg/kg IV
Prevention of bleeding associated with cardiovascular surgery	2 g IV preoperative infusion
Reduction of postpartum hemorrhage	2 g IV post vaginal delivery or cesarean section
Improvement in clot firmness after orthopedic surgery	30 mg/kg IV
Reduction of blood loss after craniosynostosis repair surgery in children	30 mg/kg IV

Adapted from references [48–60]

and headache (Table 34.4). Similar to all plasma-derived factor products, fibrinogen concentrate may also transmit disease, since the product is derived from human plasma. Monitoring parameters include fibrinogen levels and signs/symptoms of thrombosis and hypersensitivity. A target fibrinogen level of 100 mg/dL should be maintained until hemostasis occurs and wound healing is complete. The reference range for normal fibrinogen is 200–450 mg/dL [48].

Factor VIIa (Recombinant)

Brand Name (USA): NovoSeven™ RT
Description: Recombinant factor VIIa is a vitamin K-dependent glycoprotein that promotes hemostasis by activating the extrinsic pathway of the coagulation cascade. Factor VII complexes with tissue factor and activates coagulation factors IX and X. When complexed with other factors, coagulation factor Xa converts prothrombin to thrombin, a key step in the formation of a fibrin-platelet hemostatic plug. Recombinant factor VIIa has a short terminal half-life of 2.6–3.1 h, thus a need for frequent dosing. Recombinant factor VIIa is available as an intravenous solution [61].

Adult Use: Recombinant factor VIIa is indicated for use in patients with hemophilia A or B with inhibitors [61], congenital factor VII deficiency [61], acquired hemophilia [61], and Glanzmann's thrombasthenia [61]. There have been numerous studies and reports on the unlabeled use of recombinant factor VIIa in bleeding patients. The paragraph below is not an exhaustive list but rather a general summary of the use of this product in different patient populations. Recombinant factor VIIa has been reported to be used in patients with warfarin-related intracerebral hemorrhage (ICH) [62, 63], refractory bleeding after cardiac or liver surgery in nonhemophilic patients [63–67], anticoagulation reversal [68–70], blood loss reduction after cardiac surgery [71], coagulopathy reversal in isolated traumatic brain injury (TBI) [72], diffuse alveolar hemorrhage in bone marrow transplant (BMT) patients [73], bridge to transplant in end-stage liver disease patients [73], trauma-related coagulopathy [73], refractory perioperative bleeding in noncardiac patients [73], life-threatening refractory hemorrhage of any cause in severely coagulopathic patients [63, 73], blood loss reduction in abdominal trauma patients [74], and esophageal varices [63].

Pediatric Use: Recombinant factor VIIa can also be utilized in the pediatric population for reduction in blood loss and requirement for blood products after cardiac surgery [75, 76], coagulopathies [77], treatment of severe bleeding associated with dengue hemorrhagic fever [78], liver impairment [79, 80], and nonhemophilic hemorrhages [81].

Adverse Effects and Monitoring Parameters: Recombinant factor VIIa may cause antibody formation, hypersensitive reactions, thromboembolic events, and hyper- or hypotension (Table 34.5). Monitoring parameters include evidence of hemostasis. The prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (PTT), and factor VII may also be useful as adjunct tests to evaluate efficacy [61].

Desmopressin

Brand Names (USA): DDAVP™, Stimate™
Description: Desmopressin is a synthetic analogue of vasopressin, but the molecular structure is modified from vasopressin to reduce its vasoactive actions; vasopressin activates both V1 and V2 receptors where desmopressin only stimulates V2 receptors. Desmopressin increases plasma levels of von Willebrand factor (VWF), factor VIII (FVIII), and tissue plasminogen activator (t-PA) contributing to a shortened PTT and bleeding time. These effects are likely due to stimulating the release of VWF from endothelial storage sites; however, this mechanism is not fully understood, and several hypotheses exist [82–86]. The secreted t-PA is inactivated by plasminogen activator inhibitor and thus does not seem to promote fibrinolysis or bleeding. Most patients with type 1

Table 34.5 Factor VIIa dosing

Indication	Dose, frequency, and duration
Warfarin-related ICH	• 10–100 mcg/kg IV administered concurrently with IV vitamin K *Lower doses (10–20 mcg/kg) are generally preferred given the higher risk of thromboembolic complications with higher doses*
Treatment of refractory bleeding after cardiac surgery in nonhemophilic patients	• 35–70 mcg/kg IV • 10–20 mcg/kg in patients with a left ventricular assist device, to reduce thromboembolic events
Reduction in blood loss after cardiac surgery	40 mcg/kg IV
Reverse coagulopathy in patients with isolated TBI	20 mcg/kg IV *(in addition to other blood products)*
Diffuse alveolar hemorrhage in BMT patients, bridge to transplant in end-stage liver disease, trauma-related coagulopathy, refractory perioperative bleeding in noncardiac patients, life-threatening refractory hemorrhage in coagulopathic patients	30 mcg/kg IV repeated every 15 min to a maximum dose of 90 mcg/kg
Blood loss reduction in abdominal trauma patients	24–72 mcg/kg IV, repeat in 3 h if no clinical improvement
Reduction in blood loss after cardiac surgery in pediatrics	90–180 mcg/kg IV after cardiac surgery 40 mcg/kg IV during surgery
Coagulopathies in pediatrics	5 mcg/kg IV initial, followed by 10, 20, 40, or 80 mcg/kg IV
Treatment of severe bleeding associated with dengue hemorrhagic fever in pediatrics	100 mcg/kg IV × 1 (or repeated doses every 4 h as needed)
Chronic liver disease in children	38–118 mcg/kg IV × 1
Nonhemophilic hemorrhage in pediatrics	90 mcg/kg IV × 2
Usual dose range 40–90 mcg/kg IV	

Adapted from references [61–81]

von Willebrand disease (VWD) and FVIII/VWF levels greater than 10 units/mL will respond to desmopressin, but patients with type 2 VWD have a more variable response. Prior to utilizing desmopressin for therapy, a therapeutic trial should be conducted to determine a patient's response. To test responsiveness, blood samples are taken 30–60 min and 4 h after an intravenous injection of desmopressin to obtain a reliable figure on recovery and clearance of FVIII and VWF [87]. Desmopressin has an elimination half-life of 2–4 h; however, the half-life is prolonged to 9 h in patients with renal impairment (See Table 34.7) [35].

Formulations: Desmopressin is available as a 4 mcg/mL injection and a 1.5 mg/mL nasal solution. The nasal formulation is ~2.75 times less potent than the injection formulation. Therefore, the nasal solution is often used for minor bleeding, while the intravenous injection is preferred for surgical bleeding prophylaxis and major bleeding. Desmopressin is also available as an oral tablet and a rhinal tube [83].

Adult Use: Desmopressin is utilized in the treatment and prevention of bleeding episodes in mild-to-moderate hemophilia A and mild-to-moderate VWD type 1 patients who respond to a desmopressin challenge [34, 88, 89], uremia associated with acute or chronic renal failure [90], prevention of surgical bleeding in patients with uremia [91], stabilization of platelet function in intracranial hemorrhage [92], blood loss reduction after cardiac surgery [93, 94], blood loss reduction in dental procedures [83], and blood loss reduction in patients with liver cirrhosis [95–98]. It is recommended to utilize VWF in addition to desmopressin if the postsurgical treatment is necessary for more than three days [83].

Pediatric Use: In the pediatric setting, desmopressin is utilized for heavy menstrual bleeding in adolescent females [99, 100], congenital VWD in patients who respond to a desmopressin challenge [82], congenital platelet defect disorders in patients who respond to a desmopressin challenge [82], circumcision in combined factor V and VIII deficiency [101], tonsillectomy and adenoidectomy [83], and otologic surgery [83]. Studies have shown that desmopressin administered as a one-time dose after cardiopulmonary bypass failed to reduce blood loss after cardiovascular surgery in pediatrics [102–104]. Of note, children under two years of age tend to have a lower response to desmopressin in comparison to older children [83].

Adverse Effects and Monitoring Parameters: Desmopressin may cause flushing, hypo- or hypertension, headache, fatigue, hyponatremia, abdominal pain, abnormal lacrimation (intranasal formulation), conjunctivitis (intranasal formulation), and ocular edema (intranasal formulation) (Tables 34.6 and 34.7). Monitoring parameters include fluid intake, urine volume, and signs/symptoms of hyponatremia [83]. Young children may be at an increased risk for hyponatremia-induced seizures when the intravenous formulation is utilized; fluid restriction and careful monitoring of serum sodium levels and urine output are warranted [105–109].

Table 34.6 Desmopressin dosing

Indication	Dose, frequency, and duration
Uremic bleeding associated with acute or chronic renal failure	0.4 mcg/kg IV once
Prevention of surgical bleeding in patients with uremia and reduction in bleeding time in patients with liver cirrhosis	0.3 mcg/kg IV once
Reduction of blood loss in intracranial hemorrhage	24 mcg IV once • Patients 20 kg= 8 mcg • Patients 50 kg= 20 mcg • Patients 100 kg= 40 mcg or 0.3 mcg/kg
Blood loss reduction after cardiac surgery	0.3 mcg/kg IV once after coming off cardiopulmonary bypass
Dental procedure	0.3 mcg/kg IV daily for 1–2 days
Heavy menstrual bleeding in adolescent females	Intranasal desmopressin: 1.5 mg/mL or 150 mcg per spray 1 spray < 50 kg; 2 sprays ≥ 50 kg Administered once daily started at onset of menses and continued for subsequent 2 days after menses
Hemophilia A and von Willebrand disease in infants ≥11 months, children, adolescents, and adults	Intranasal desmopressin: 1.5 mg/mL or 150 mcg per spray Patients < 50 kg: 150 mcg (1 spray) Patients ≥ 50 kg: 300 mcg (1 spray each nostril) If using preoperatively, administer 2 h before surgery
Congenital VWD and congenital platelet defect disorders in pediatrics	0.3 mcg/kg IV once, if used preoperatively administer 30 min before procedure; may repeat dose if needed
Tonsillectomy, adenoidectomy, and otologic surgery in pediatrics	0.3 mcg/kg IV once or twice daily for 1–7 days
Generally, 0.3 mcg/kg of desmopressin can increase the level of FVIII and von Willebrand factor for two- to sixfold. Peak effect occurs 1 h after injection. Recommended not to use more than once daily due to development of tachyphylaxis [34]	

Adapted from references [34, 83, 88, 101]

Table 34.7 Desmopressin dosing in renal impairment

Creatinine clearance	Dose
<50 mL/min	Contraindicated (except 1.5 mg/mL nasal spray)
However, it has been used in acute and chronic renal failure patients experiencing uremic bleed or prevention of surgical bleeding	

Adapted from references [34, 90, 91]

Due to the risk of hyponatremia, some institutions adopt sodium limits associated with desmopressin administration, i.e., avoid desmopressin if sodium is less than 130 meq/L. Tachyphylaxis can occur with consecutive dosing of desmopressin; thus, it is recommended to use specific factor concentrates or platelet transfusions, depending on the underlying disease, if hemostasis after major trauma or surgery is desired [110].

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Brand Name (USA): Humate-P™
Description: Humate-P™ is a factor product that is derived from human plasma and contains FVIII, VWF, and small amounts of fibrinogen and albumin [111]. Its use is primarily to replace endogenous factor VIII and VWF in patients with hemophilia A or VWD. Factor VIII in conjunction with activated factor IX activates factor X which converts prothrombin to thrombin and fibrinogen to fibrin. VWF promotes platelet aggregation and adhesion to damaged vasculature and acts as a carrier protein for factor VIII. Circulating levels of functional VWF are measured as ristocetin cofactor (VWF:RCo) activity. The average ratio of VWF:RCo to FVIII in Humate-P™ is 2.4:1, which is more similar to the ratio in normal human plasma in comparison to other VWF/FVIII products. The elimination hale-life of VWF:RCo in Humate-P™ has a wide range of 3–34 h in patients with VWD. Humate-p™ is available as an intravenous powder for reconstitution [112].

Adult Use: Humate-P™ is utilized in adult patients for the prevention and treatment of bleeding episodes in patients with hemophilia A [111]); treatment of spontaneous or trauma-induced bleeding and prevention of excessive bleeding during and after surgery in patients with severe VWD [111, 113, 114], including mild or moderate disease where use of desmopressin is known or suspected to be inadequate [111]); reduction of postpartum blood loss in VWD type 3 patients [115]; and development of acquired von Willebrand disease after ventricular assist device implantation [112]. When used for surgical prophylaxis, target levels of VWF:RCo should be approximately 100 units/dL and, at

Table 34.8 Antihemophilic factor/von Willebrand factor complex dosing (Humate-P™)

Indication	Dose, frequency, and duration
Treatment and prophylaxis of bleeding episodes	Dose, frequency, and duration are based on severity of bleed
Prophylaxis prior to surgical and/or invasive procedures	Dose, frequency, and duration are based on severity of surgery
Acquired VWD after ventricular assist device implantation	60 units/kg IV every 8 h for three doses; then 60 units/kg IV every 12 h; then 40 units/kg IV every day and unfractionated heparin started to maintain PTT of 50 to prevent LVAD clotting
Reduction of postpartum blood loss in VWD type 3 patients	40–60 units VWF:RCo/kg IV TID or QID
Treatment of VWD in pediatrics and valproate-associated acquired von Willebrand syndrome	10–20 units VWF:RCo/kg IV for type 1 and 20–50 units VWF:RCo/kg IV for type 3 VWD either once or twice daily for 3 days
Dose and duration of treatment depend on the site and severity of bleeding. Subsequent dosing is generally based on the half-life of 8–12 h [34]	

Adapted from references [83, 111–117]

Table 34.9 Antihemophilic factor/von Willebrand factor complex dosing (Alphanate™)

Indication	Dose, frequency, and duration
Treatment and prophylaxis of bleeding episodes	Dose, frequency, and duration are based on severity of bleed
Prophylaxis prior to surgical and/or invasive procedures	Dose, frequency, and duration are based on severity of surgery

Adapted from references [83, 118–120]

least for the first 3 days of treatment, a nadir of 50 units/dL VWF:RCo, as well as similar targets for FVIII [83]. Humate-P™ administered as a continuous infusion has also been reported to be successful for surgical prophylaxis [83].

Pediatric Use: Humate-P™ is utilized in pediatric patients with VWD undergoing surgery, bleeding events in VWD [116, 117], prophylaxis in VWD [116], and valproate-associated von Willebrand syndrome [117].

Adverse Effects and Monitoring Parameters: Adverse effects of Humate-P™ include antibody formation, hypersensitivity, thrombotic events, rash, dizziness, headache, and nausea/vomiting (Table 34.8). Monitoring parameters include heart rate, blood pressure, AHF levels prior to and during treatment, inhibitor development, hematocrit, signs/symptoms of intravascular hemolysis, bleeding, and VWF activity. In surgical patients, monitor VWF:RCo at baseline and after surgery and trough VWF:RCo and FVIII:C daily. Humate-P™ can also transmit infections since it's derived from human plasma [111].

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Brand Name (USA): Alphanate™
Description: Alphanate™ is derived from human plasma and contains FVIII, VWF, and other plasma proteins. Alphanate™ is used to replace endogenous factor VIII and VWF. The average ratio of VWF:RCo to FVIII in Alphanate™ is not provided by the manufacturer but is approximately 1:1. Of note, Alphanate™ has less VWF per unit when compared with Humate-P™. The elimination half-life range for Alphanate™ is the same as Humate-P™ (3–34 h). Alphanate™ is available as an intravenous powder for reconstitution [83].

Adult Use: Alphanate™ is utilized for the prevention and treatment of hemorrhagic episodes in patients with hemophilia A [118] and prophylaxis with surgical and/or invasive procedures in patients with VWD when desmopressin is either ineffective or contraindicated [118, 119]. Alphanate™ is not indicated for surgical prophylaxis in patients with severe VWD, type 3 [83, 118].

Pediatric Use: Alphanate™ is used in pediatric patients with VWD for the treatment of bleeding episodes [120] and prophylaxis prior to surgery [118, 120].

Adverse Effects and Monitoring Parameters: Alphanate™ can cause antibody formation, hypersensitivity, thrombotic evens, rash, face edema, headache, dizziness, and nausea (Table 34.9). Alphanate™ can also cause transmission of infections since it is derived from human plasma. Monitoring parameters are the same as those listed for Humate-P™.

Phytonadione (Vitamin K)

Brand Name (USA): Mephyton™
Description: Phytonadione is a vitamin that is necessary for the liver to synthesize factors II, VII, IX, and X. These vitamin-K dependent coagulation factors are γ-carboxylated by the action of vitamin K and glutamyl carboxylase. Phytonadione is available as an intravenous aqueous colloidal solution and an oral tablet [121].

Table 34.10 Phytonadione dosing

Indication	Dose, frequency, and duration
Hypoprothrombinemia due to drugs or factors limiting absorption or synthesis	Oral, subQ, IM, IV: initial: 2.5–25 mg (rarely up to 50 mg)
Vitamin K deficiency (supratherapeutic INR) secondary to VKAs	INR 4.5–10 (no bleeding): 2012 ACCP guidelines recommend against routine phytonadione administration. Others recommend consideration of phytonadione 1 mg PO or 0.5 mg IV INR >10 (no bleeding): 2012 ACCP guidelines recommend against administration of phytonadione. Others recommend consideration of phytonadione 2–2.5 mg PO or 0.5–1 mg IV If minor bleeding at any INR elevation: hold warfarin, may administer phytonadione 2.5–5 mg PO; monitor INR more frequently, may repeat dose after 24 h if INR correction incomplete; resume warfarin at an appropriately adjusted dose when INR is in desired range If major bleeding at any INR elevation: the 2012 ACCP guidelines recommend administration of four-factor prothrombin complex concentrate and phytonadione 5–10 mg IV
Preprocedural/surgical INR normalization in patients receiving warfarin	1–2.5 mg PO once administered on the day before surgery; recheck INR on day of procedure/surgery
Bleeding in pediatric patients with chronic cholestasis	5 mg IV once

Adapted from references [121–126]

Adult Use: Phytonadione is used in the prevention and treatment of hypoprothrombinemia caused by vitamin K antagonist (VKA)-induced or other drug-induced vitamin K deficiency [121], hypoprothrombinemia due to drugs or factors limiting absorption or synthesis [121], vitamin K deficiency secondary to VKA [122–124], and preprocedural/surgical INR normalization in patients receiving warfarin [122, 125].

Pediatric Use: Phytonadione is used in pediatric patients to treat vitamin K deficiency secondary to vitamin K antagonist administration [121] and bleeding in patients with chronic cholestasis [126].

Adverse Effects and Monitoring Parameters: Phytonadione can cause hypersensitivity reactions, flushing, dizziness, and abnormal taste (Table 34.10). PT, INR, and hypersensitive reactions should be monitored following phytonadione administration [121].

Four-Factor Prothrombin Complex Concentrate (Human)

Brand Name (USA): Kcentra™
Description: Kcentra™ is derived from human plasma and contains factors II, VII, IX, and X proteins C and S. Coagulation factors II, IX, and X are part of the intrinsic coagulation pathway, while factor VII is part of the extrinsic coagulation pathway. Ultimately, these factors facilitate the activation of prothrombin into thrombin which converts fibrinogen into fibrin resulting in clot formation. Proteins C and S are vitamin K-dependent inhibiting enzymes involved in regulating the coagulation process. Protein S serves as a cofactor for protein C, which is converted to activated protein C (APC). APC is a serine protease that inactivates factors Va and VIIIa, limiting thrombotic formation. The elimination half-life of this product is dependent on the half-life of its individual components: factor II, 48–60 h; factor VII, 1.5–6 h; factor IX, 20–24 h; factor X, 24–48 h; protein C, 1.5–6 h; and protein S, 24–48 h. Kcentra™ is available as an intravenous powder for reconstitution [127]. Three-factor prothrombin complex concentrates (Bebulin™ and Profilnine™) differ from Kcentra in that they do not contain factor VII but only contain factors II, IX, and X (see Tables 34.12 and 34.13) [128–130].

Adult Use: Kcentra™ is indicated for VKA reversal in patients with acute major bleeding or need for an urgent surgery/invasive procedure [127]. Reports have also shown Kcentra™ to be effective in the reversal of direct factor Xa anticoagulants [131, 132], an alternative agent to fresh frozen plasma (FFP) in patients with serious/life-threatening bleeding related to vitamin K antagonist therapy [133], and in acquired, non-warfarin-related coagulopathy in major trauma and surgery [134–137].

Pediatric Use: Data supporting four-factor prothrombin complex concentrate use in pediatric patients is limited to case reports or case series. These data show prothrombin complex concentrate can be used for prophylaxis in patients with severe congenital factor X deficiency [138, 139] and in dilutional coagulopathy [140]. Prothrombin complex concentrate may also be useful in pediatric patients with limited total blood volume and high risk of volume overload; however, there have been no formal studies validating this.

Adverse Effects and Monitoring Parameters: Kcentra™ can cause hypersensitivity reactions, hypercoagulopathy, hypo- or hypertension, tachycardia, headache, and nausea/vomiting (Tables 34.11, 34.12, and 34.13). Infection can also be transmitted since Kcentra™ is derived from human plasma. The INR should be monitored at baseline and at 30 min post dose, and a patient's clinical response should be monitored during and after treatment [127].

Table 34.11 Four-factor prothrombin complex concentrate dosing

Indication	Dose and frequency	Duration
Vitamin K antagonist (VKA) reversal in patients with acute major bleeding or need for an urgent surgery/invasive procedure	• Pretreatment INR: 2 to <4: • 25 units/kg IV (max: 2500 units) • Pretreatment INR: 4–6: • 35 units/kg IV (max: 3500 units) • Pretreatment INR: >6: • 50 units/kg IV (max: 5000 units)	Repeat dosing is not recommended (has not been studied)
Reversal of direct factor Xa anticoagulants	50 units/kg IV	Once
Serious/life-threatening bleeding related to vitamin K antagonist therapy	25–50 units/kg IV	Once
Acquired, non-warfarin-related coagulopathy in major trauma and surgery	20–40 units/kg IV	Once
Prophylaxis in patients with severe congenital factor X deficiency in pediatrics	• 15 units/kg IV every 8–12 h in perioperative period, 20 units/kg IV every 72 h for prophylaxis • 25 units/kg IV every 72 h • 30 units/kg IV every 72 h • 30 units/kg IV twice per week	
Dilutional coagulopathy in pediatrics	30 units/kg IV	Once

Adapted from references [127, 131–140]

Table 34.12 Four-factor prothrombin complex concentrate components

Ingredient	Amount per 500 unit vial
Total protein	120–280 mg
Factor II	380–800 units
Factor VII	200–500 units
Factor IX	400–620 units
Factor X	500–1020 units
Protein C	420–820 units
Protein S	240–680 units
Heparin	8–40 units
Antithrombin	4–30 units
Human albumin	40–80 mg
Sodium chloride	60–120 mg
Sodium citrate	40–80 mg

Adapted from reference [127]

Table 34.13 Comparison of three- and four-factor prothrombin concentrations

	Kcentra™ 500 unit vial	Bebulin™ 200–1200 unit vial	Profilnine™[a] 500 unit vial
Factor II	380–800 units	480–760 units	NMT 150 units/100 units factor IX
Factor VII	200–500 units	<100 units	NMT 35 units/100 units factor IX
Factor IX	400–620 units	480–760 units	100 units
Factor X	500–1020 units	480–760 units	NMT 100 units/100 units factor IX
Heparin	8–40 units	≤72–114 units	
Protein C	420–820 units		
Protein S	240–680 units		
Antithrombin	4–30 units		

Adapted from references [127–130]
NMT not more than
[a]Also contains polysorbate 80

Thrombin Powder

Brand Name (USA): Recothrom™
Description: Thrombin is a topical product that is made through recombinant DNA technology. Thrombin activates platelets and catalyzes the conversion of fibrinogen to fibrin to promote hemostasis. Thrombin is available as a topical powder for reconstruction, topical pad, topical solution, and topical sponge [141].

Adult Use: Thrombin is utilized for hemostasis [141]; control of localized, accessible bleeding from lacerated tissues [34]; con-

trol of bleeding after dental extractions or at surgical sites [34]; and reduction of blood loss in total knee arthroplasty [142].

Pediatric Use: Thrombin powder has been studied in pediatric patients and is approved to aid in hemostasis, specifically in burn patients [141].

Adverse Effects and Monitoring Parameters: Patients who receive thrombin powder should be monitored for abnormal hemostasis (Table 34.14). Thrombin powder may also cause pruritus. Of note, this product is for topical use only [141].

Protamine Sulfate

Brand Name (USA): Not applicable
Description: Protamine is a strongly alkaline substance and is derived from the sperm of salmon and other fish species. When protamine is administered alone, it has anticoagulant effects. However, when protamine is administered in the presence of heparin, a strong acidic medication, a stable salt is formed, and the anticoagulant activity of both medications is lost. Protamine has a very rapid onset of action (5 min), and the elimination half-life is approximately 7 min. However, when protamine is administered, it neutralizes the heparin; therefore, subsequent doses are not usually required. Protamine is available as an intravenous solution [143].

Adult Use: Protamine is utilized in adults for the reversal of heparin and low molecular weight heparins [143, 144]. When heparin is given as a continuous IV infusion, only heparin given in the preceding several hours should be considered when administering protamine [145]. Protamine can also be utilized for low molecular weight heparin (LMWH) overdose, but the anti-Xa activity is never completely neutralized [146–148]. Protamine is also used to neutralize heparin in patients previously on cardiopulmonary bypass, the most effective dosing being individualized management [149], and to reduce bleeding complications after carotid endarterectomy [150].

Pediatric Use: Protamine is utilized in the pediatric patient to reverse heparin and low molecular weight heparin, to neutralize heparin from combined estimated blood volume of the patient and cardiopulmonary bypass circuit [151, 152], and to treat severe post-reperfusion coagulopathy in liver transplant patients [153].

Adverse Effects and Monitoring Parameters: Severe hypotension can occur with rapid administration of protamine; thus, protamine should be administered over at least a 10-min period (Table 34.15). Transient hypotension can still be expected within 3–4 min after administration [154]. There is also a risk for anaphylaxis with protamine administration

Table 34.14 Thrombin powder dosing

Indication	Dose, frequency, and duration
Hemostasis	Apply powder directly to the site of bleeding or on oozing surfaces

Adapted from References [34, 141, 142]

Table 34.15 Protamine dosing

Indication	Time since last heparin dose (min)	Dose of protamine (mg) IV to neutralize 100 units of heparin
Intravenous heparin overdose in adults and pediatrics	<30	1
	30–60	0.5–0.75
	60–120	0.375–0.5
	>120	0.25–0.375
Subcutaneous heparin overdose	*Not reported*	1–1.5 mg given
Severe post-reperfusion coagulopathy in liver transplant patients	*Not reported*	0.5 mg
Enoxaparin overdose in adults	≤8 h	The dose of protamine should equal the dose of enoxaparin
	>8 h or if a second protamine dose is needed	0.5 mg protamine for every 1 mg enoxaparin
Dalteparin or tinzaparin in adults	*Not reported*	1 mg protamine for every 100 anti-Xa units of dalteparin or tinzaparin. If PTT is prolonged 2–4 h after the first dose or if bleeding continues, consider additional doses of 0.5 mg for each 100 anti-Xa unit
Low molecular weight heparin	≤4 h	The dose of protamine should equal the dose of LMWH. If the PTT is still prolonged 2–4 h after the initial dose, a second dose of 0.5 mg protamine per 1 mg LMWH may be administered
Each milligram of protamine sulfate neutralizes not less than 100 units of heparin. Doses should not exceed 50 mg. Since heparin is rapidly cleared from the circulation, the dose of protamine required decreased with the time elapsed following heparin administration		

Adapted from references [143–153]

secondary to histamine release, which has been reported mainly during cardiac surgeries [155]. Since protamine has weak anticoagulant activity, due to an interaction with platelets and proteins including fibrinogen, protamine overdose can cause bleeding. This effect should be distinguished from the rebound anticoagulation that may occur 30 min to 18 h following the reversal of heparin with protamine [143].

Anti-inhibitor Coagulant Complex (Human)

Brand Name (USA): Feiba NF™
Description: Anti-inhibitor coagulant complex is a human plasma-derived factor product and contains nonactivated factors II, IX, and X and activated factor VII. Anti-inhibitor coagulant complex also contains factor VIII bypassing activity at approximately equal unitages to the other factors and 1–6 units of factor VIII coagulant antigen per milliliter. Anti-inhibitor coagulant complex shortens the activated partial thromboplastin time of plasma containing factor VIII inhibitor. Strengths are expressed in terms of factor VIII inhibitor bypassing activity, and one unit of activity is defined as the amount of anti-inhibitor coagulant complex that shortens the PTT of a high-titer factor VIII inhibitor reference plasma to 50 % of the blank value. The elimination half-life of anti-inhibitor coagulant complex is approximately 4–7 h. Anti-inhibitor coagulant complex is available as an intravenous powder for reconstitution [156].

Adult Use: Anti-inhibitor coagulant complex is utilized in adults for control and prevention of bleeding episodes in hemophilia patients with inhibitors [156] and moderate to severe bleeding in patients with acquired hemophilia [157, 158]. Anti-inhibitor coagulant complex is also used for perioperative management in hemophilia patients with inhibitors, life-threatening bleeding associated with dabigatran use [159–165], and life-threatening bleeding associated with rivaroxaban use [166]; reversal of warfarin-related bleeding [167]; and management of refractory bleeding in cardiac surgery [168].

Pediatric Use: Anti-inhibitor coagulant complex is utilized in pediatrics for control and prevention of bleeding episodes in hemophilia patients with inhibitors [156], prevention of bleeding episodes in factor X deficiency [169], and treatment of hemothorax in children with congenital coagulopathy [170].

Adverse Effects and Monitoring Parameters: Thrombotic and thromboembolic events can occur following anti-inhibitor coagulant complex use, especially with doses ≥ 100 units/kg (Table 34.16). Therefore, caution is advised in patients with atherosclerotic disease, crush injury, septicemia, or concomitant treatment with factor VIIa or antifibrinolytics due to increased risk of developing thrombotic events from circulating tissue factor or predisposing coagulopathy. Infection can also be transmitted since anti-inhibitor coagulant complex is derived from human plasma. Monitoring parameters include

Table 34.16 Anti-inhibitor coagulant complex dosing

Indication	Dose, frequency, and duration
Joint hemorrhage in adult and pediatric hemophilia patients with inhibitors	50–100 units/kg IV every 12 h until pain improves (max 200 units/kg/day)
Mucous membrane bleeding in adult and pediatric hemophilia patient inhibitors	50–100 units/kg IV every 6 h for at least 1 day or until bleeding resolves (max 200 units/kg/day)
Soft tissue bleeding and other severe bleeding in adult and pediatric hemophilia patients with inhibitors	100 units/kg IV every 12 h until bleeding resolves (max 200 units/kg/day)
Moderate to severe bleeding in adults due to acquired hemophilia	50–100 units/kg IV every 8–12 h until bleeding resolves
Perioperative management in adult and pediatric hemophilia patients with inhibitors	50–100 units/kg IV administered immediately preoperative then 50–100 units/kg IV every 6–12 h until bleeding is resolved and healing achieved (max 200 units/kg/day)
Routine prophylaxis in adults and pediatric hemophilia patients with inhibitors	85 units/kg IV every other day
Life-threatening bleeding associated with dabigatran use in adults	25–100 units/kg IV
Life-threatening bleeding associated with rivaroxaban use in adults	30 units/kg IV
Prevention of bleeding episodes in pediatric patients with factor X deficiency	74 units/kg IV once weekly *This therapy should be individually tailored to each patient*
Reversal of warfarin-related bleeding in adults	INR < 5: 500 units IV INR ≥ 5: 1000 units IV Intravenous vitamin K also administered concomitantly
Refractory bleeding management in adult patients undergoing cardiac surgery	1225 units IV
Hemothorax in children with coagulopathy	100 units/kg IV every 12 h for 3 days, then 100 units/kg IV every 24 h for 4 days

Adapted from references [156–170]

signs of symptoms of DIC, hemoglobin, and hematocrit. Of note, PTT and thromboelastography (TEG) should not be utilized to monitor response; DIC can occur when practitioners attempt to normalize these values with anti-inhibitor coagulant complex [156].

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