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Management of Inherited, Acquired, and Iatrogenically Induced Coagulopathies in Oral Surgery

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Additional information is available at the end of the chapter

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Abstract

Hemostasis is the process of cessation of blood loss. Alterations of the hemostatic pathways can result in a hypercoagulable or hypocoagulable state resulting in thrombosis or hemorrhage. Common defects in hemostasis and their management, specifically the hypocoagulable state, are discussed as these defects often result in increased perioperative blood loss, which can result in compromised patient outcomes.

Keywords: hemostasis, platelets, coagulation, bleeding, hemophilia, von Willebrand disease, warfarin, Coumadin, heparin, fondaparinux, Arixtra, Aspirin, PGI₂ blockers, clopidogrel, ticagrelor, direct oral anticoagulants, dabigatran, Pradaxa, rivaroxaban, Xarelto, apixaban, Eliquis, thrombocytopenia, ITP, liver disease, kidney disease, Surgicel, Gelfoam, topical thrombin, HemCon, CollaPlug, tranexamic acid, aminocaproic acid

1. Introduction

The process of hemostasis can be divided into four phases namely formation of the platelet plug, clot development via the coagulation cascade, termination of the coagulation cascade, and clot fibrinolysis [1]. The formation of the platelet plug can be described as primary hemostasis. Clot development via the coagulation cascade is subsequently termed secondary hemostasis. Primary hemostasis occurs immediately following endothelial cell damage and includes a vascular phase and a platelet phase. The vascular phase occurs following vascular injury and results in the vasoconstriction of the blood vessel. The platelet phase follows the vascular phase and consists of the formation of the initial platelet plug.

The formation of the platelet plug includes activation, adhesion, and aggregation. Platelet activation occurs via exposure of platelets to subendothelial collagen [2]. This results in a conformational change of the platelets as well as a release of granules within the platelets. This is followed by platelet adhesion to the subendothelial collagen in damaged blood vessels via von Willebrand's factor (VWF) and GP1b [3]. Platelet activation and the production of platelet products including thromboxane A₂, ADP, and serotonin result in a conformational change in GPIIb/IIIa on platelets that allows platelets to bind to fibrinogen resulting in platelet aggregation (Figure 1) [4].

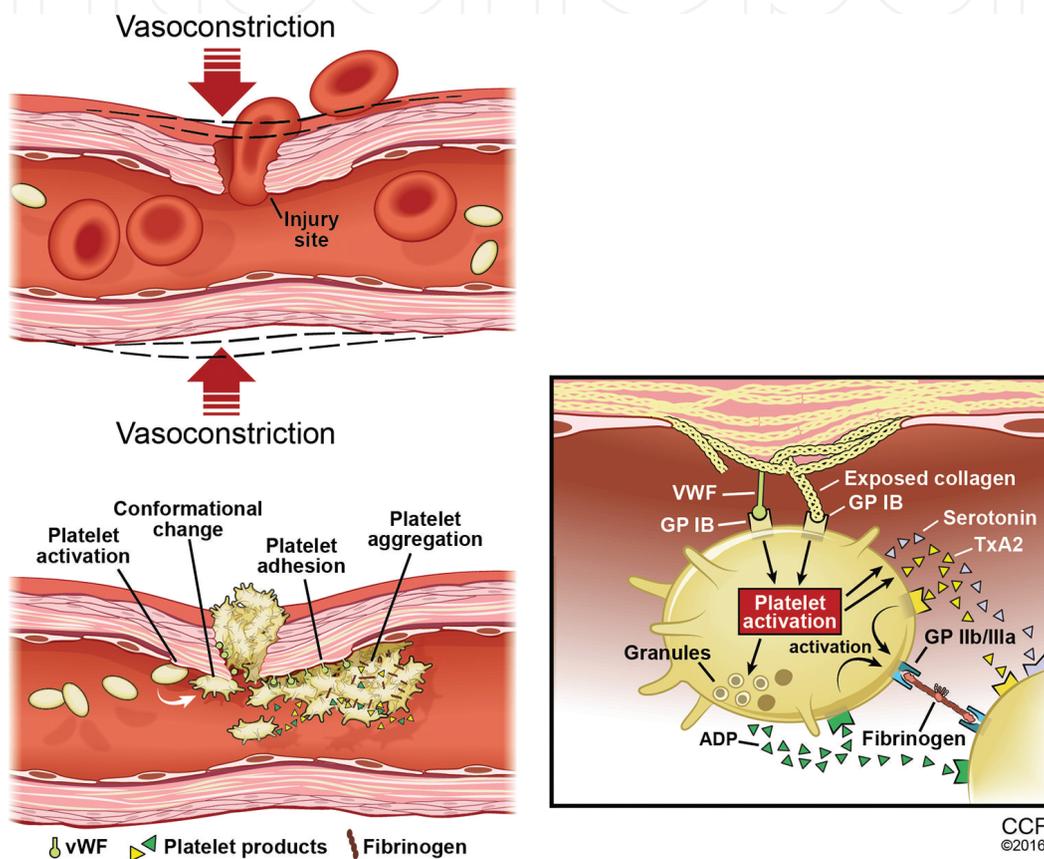


Figure 1. Primary hemostasis.

Secondary hemostasis results in clot development via the coagulation cascade, in which activation of serine protease zymogens results in the conversion of fibrinogen to fibrin and the cross-linking of fibrin that stabilizes the initial platelet plug. Traditionally, the coagulation cascade is broken down into the extrinsic and intrinsic pathways. The extrinsic pathway is initiated when tissue factor from damaged endothelial cells within the disrupted vasculature binds to factor VII, leading to the activation of factor X and the common pathway of the coagulation cascade. In the intrinsic pathway, activation of high molecular weight kininogen, conversion of prekallikrein to kallikrein, and activation of factors XII, XI, IX, and VIII leads to the activation of factor X and the common pathway of the coagulation cascade. The common pathway includes the activation of factors X, V, thrombin, and the conversion of fibrinogen to

fibrin by thrombin, resulting in the formation of the fibrin clot. Thrombin also upregulates other upstream clotting factors including V, VIII, and XI, further promoting the formation of thrombin and the fibrin clot via the extrinsic pathway [5]. Termination of the coagulation cascade occurs via activation of antithrombin, tissue factor inhibitor, thrombomodulin, protein C, and protein S [6, 7]. In the fibrinolytic phase, plasminogen is converted to plasmin via tissue plasminogen activator. The effect of plasmin is to cleave fibrin and fibrinogen leading to the dissolution of the clot (**Figures 2 and 3**) [8].

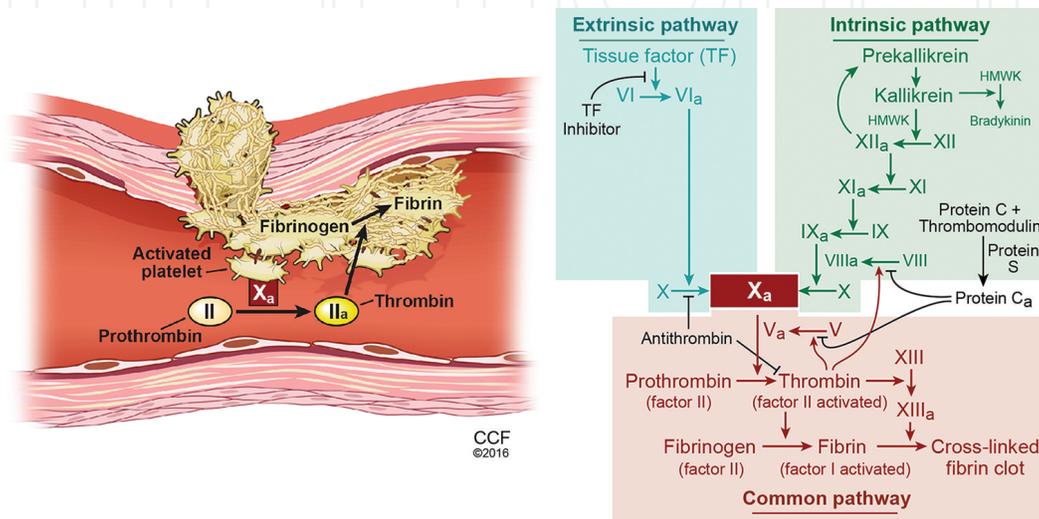


Figure 2. Extrinsic/intrinsic pathways. Termination of coagulation cascade.

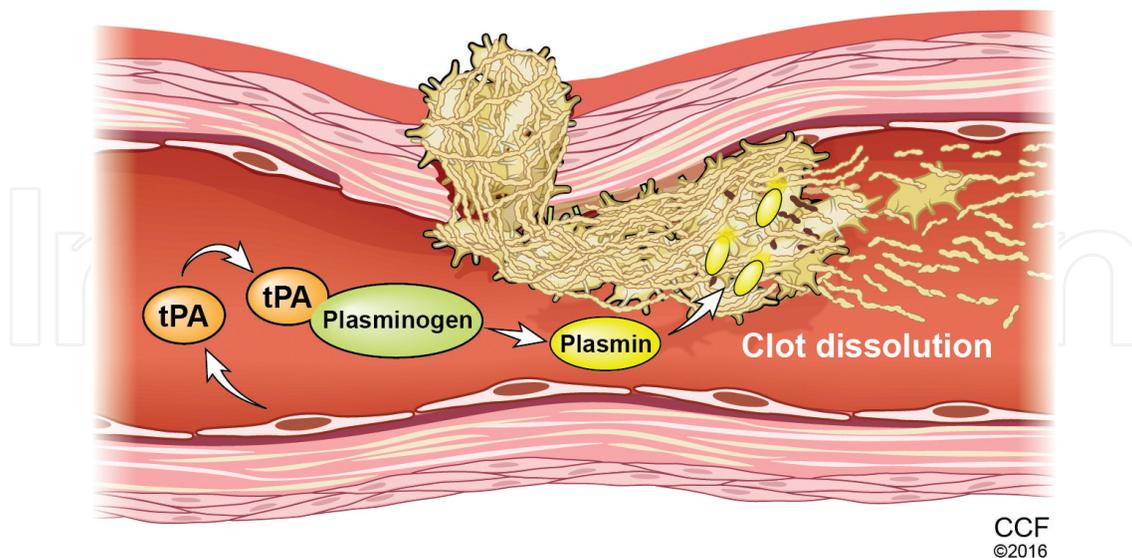


Figure 3. Fibrinolysis.

This chapter deals with the management of inherited, acquired, and iatrogenically induced coagulopathies in oral surgery.

2. Inherited and Acquired Coagulopathies

2.1. Overview

As hemostasis occurs via primary and secondary mechanisms, coagulopathies can be divided into similar categories. Defects in primary and secondary hemostasis typically have different presentations. Characteristically, primary hemostatic disorders, or defects in platelet function, result in mucocutaneous bleeding such as epistaxis, petechiae, menorrhagia, and ecchymosis [9]. Secondary hemostatic disorders, or defects in the coagulation cascade, result in deep bleeding such as hematomas and hemarthroses. Disorders of hemostasis can also be divided into congenital and acquired disorders of hemostasis. Acquired disorders are the most common cause of prolonged bleeding. In contrast to the congenital disorders in which only one factor is typically affected, the acquired coagulation disorders often have multiple factors affected. Congenital disorders of primary hemostasis include platelet function disorders (**PFDs**) and von Willebrand disease (VWD). Congenital disorders of secondary hemostasis include hemophilias A and B. Acquired disorders of hemostasis include immune thrombocytopenia (ITP), uremia-induced platelet dysfunction, defects due to chronic liver failure, and iatrogenic or medication-induced coagulopathies (**Tables 1 and 2**).

	Minor surgery		Major surgery		Mild renal impairment	Moderate renal impairment
	Pre-op	Post-op	Pre-op	Post-op		
Warfarin	INR <3.0	Adequate hemostasis/ next morning	Hold 5 days	Adequate hemostasis/ next morning		
Heparins						
Heparin	4–6 h	Once hemostasis achieved	4–6 h	48–72 h		
LMWH	24 h	24 h	24 h	48–72 h		
Fondaparinux	48 h	24 h	96 h	24 h	72–120 h	72–144 h
Platelet inhibitors						
Aspirin	None	None	None	None		
Clopidogrel	None	None	None	None		
Dual -antiplatelet therapy	None	None	None	None		

	Minor surgery		Major surgery		Mild renal impairment	Moderate renal impairment
	Pre-op	Post-op	Pre-op	Post-op		
Direct anticoagulants						
Dabigatran	48 h, PT or PTT compared to normal <1.2X	24 h	72 h, PT or PTT compared to normal <1.2X	48–72 h	48–72 h	72–120 h
Rivaroxaban	48 h, PT:PTT <1.2×	24 h	72 h, PT:PTT <1.2×	48–72 h	48–72 h	72–96 h
Apixaban	48 h	24 h	72 h	48–72 h	48–72 h	72–96 h

*Determination to bridge based on risk for thromboembolism in consultation with cardiologist.

**In patients with low risk for cardiovascular event aspirin may be discontinued 7–10 days prior to surgery.

***There are no RCTs evaluating bleeding risk with dental extractions.

Table 1. Perioperative management of antithrombotic therapy.

Hemostatic agent	Description	Features
Gelfoam	Gelatin sponge	Highly absorptive Matrix for coagulation cascade Neutral pH can be used in combination with topical thrombin
Surgicel	Oxidized regenerated cellulose	Bactericidal Acidic pH should not be used with topical thrombin Reported negative effect on nerve function
CollaCote, CollaTape, CollaPlug	Collagen product	Highly absorptive Matrix for coagulation cascade
Topical thrombin	Converts fibrinogen to fibrin	Converts fibrinogen to fibrin in final step of coagulation cascade Gelfoam can be soaked in liquid thrombin for increased hemostasis
Tranexamic acid	Inhibits conversion of plasminogen to plasmin	Gauze soaked in 5% tranexamic acid liquid for hemostasis Liquid 4.8% tranexamic acid q6h 2–5 days as postoperative mouth rinse for hemostasis
HemCon	Chitosan agent	Antimicrobial properties Sutures not required for placement

See Refs. [100, 164].

Table 2. Local hemostatic agents.

2.2. Inherited disorders of hemostasis

2.2.1. Platelet function disorders (PFDs)

Platelets are anucleate cellular fragments derived from megakaryocytes. Platelets are produced via the activation of the hormone thrombopoietin (TPO), have an average life span of 7–10 days, and are critical to primary hemostasis. The normal blood cell count of platelets is 150,000–450,000/ μl [10]. When endothelial injury occurs, von Willebrand's factor is able to bind to subendothelial collagen. Platelets then bind to von Willebrand's factor, the platelet GP1b glycoprotein. Platelet activation via exposed collagen and other platelet agonists is followed by aggregation via GPIIb/IIIa. Platelet activation leads to the secretion of thromboxane and the secretion of ADP and serotonin from the dense granules. This further promotes platelet activation and aggregation that propagates primary hemostasis [2–4, 9].

Historically, von Willebrand disease has been identified as the most common inherited defect of primary hemostasis, but recent studies suggest that platelet function disorders (PFDs) may actually be more common [11]. Individuals with PFDs commonly have symptoms of abnormalities in primary hemostasis including mucocutaneous bleeding, ecchymosis, menorrhagia, and epistaxis [9]. Severe forms of PFDs are rare and include Bernard-Soulier syndrome, a deficiency in GP1b, and Glanzmann thrombasthenia, a deficiency in GPIIb/IIIa. Less severe forms of platelet function disorder are more common and may include defects in receptors, platelet agonists, platelet storage granule defects, and signal transduction defects [9].

Traditionally, bleeding time was used to evaluate platelet function, but this has fallen out of favor. The platelet function screen (PFS) is used more often today and is readily available at most hospitals. The downside of the PFS is its low sensitivity, especially in cases of mild platelet function defect [12]. The best test for diagnosis of platelet function disorders is light transmission aggregometry (LTA), in which platelet aggregation is promoted via agonists leading to an increase in light transmission that can be quantified [12]. However, LTA is not readily available and is thus rarely utilized in clinical testing. Due to the limitations of clinical diagnostic testing as noted above, patients with symptoms of mucocutaneous bleeding without laboratory abnormalities may not be diagnosed. These patients can be identified as having mucocutaneous bleeding of unknown cause [9]. In patients with platelet function disorders, the use of local measures and antifibrinolytics, such as a 5% tranexamic acid mouthwash every 4–6 h perioperatively, should be a mainstay of therapy for patients undergoing oral surgery procedures. If moderate bleeding is expected, desmopressin at a dose of 0.3 $\mu\text{g}/\text{kg}$ (max dose 20 μg) can be administered intravenously 1 h prior to procedure [13]. In patients with severe risk of bleeding or severe forms of PFDs, such as Bernard-Soulier syndrome or Glanzmann thrombasthenia, perioperative platelet transfusion may be indicated. Platelet transfusions are rarely used for patients with mild forms of PFDs [13]. Some risks associated with platelet transfusions include the development of HLA antibodies or antibodies to platelet glycoproteins. Additional risks of blood components include the transmission of infectious diseases, which is discussed.

2.1.2. Von Willebrand disease

Von Willebrand disease (VWD) has been historically identified as the most common inherited bleeding disorder. VWD is caused by an inherited defect in the concentration, structure, or function of von Willebrand's factor [14]. VWD can be the result of a qualitative or quantitative defect in VWF. The prevalence of all types of VWD is estimated to be around 1 in 100 [15]. VWF is synthesized in vascular endothelial cells and megakaryocytes. Within the endothelial cells, VWF can be stored in Weibel-Palade bodies or released directly from the endothelial cells. In platelets, VWF is stored in the alpha-granules [16]. VWF plays a role in both primary and secondary hemostasis, and therefore, VWD may include symptoms of defects in both primary and secondary hemostasis. In primary hemostasis, VWF promotes subendothelium binding to platelets via GP1b. VWF further promotes binding between platelets via GPIIb. During secondary hemostasis, VWF stabilizes Factor VIII, promoting the coagulation cascade [17].

Type I VWD is the most common form of VWD, accounting for 60–80% of all cases. It is defined by 10–45% of circulating levels of VWF. Type I VWD is also inherited in an autosomal-dominant fashion, but is usually found incidentally during a surgical procedure.

Type II VWD is usually an inherited autosomal-dominant disorder and is considered a qualitative disorder. Subtypes of Type II VWD include IIA, IIB, IIM, and IIN. Type IIA VWD is due to a defect in the synthesis of high and medium molecular weight VWF multimers or an increase cleavage of VWF by ADAMS13 [17]. Type IIB VWD is caused by a gain-of-function mutation in the GPIb binding site of VWF. This results in activation of VWF and platelet aggregation, followed by clearance of VWF and platelets. Patients with Type IIB VWD may present with thrombocytopenia [17]. Type IIM is due to a decrease in interaction between VWF and platelets [17]. Type IIN is inherited in an autosomal recessive manner and is due to a mutation in the factor VIII binding site of VWF [17].

Type III VWD is inherited in an autosomal recessive manner and is considered the most severe form of VWD, as no VWF is produced [15]. There is great inter-individual variability between the different types and subtypes of VWD, resulting in variable risks of hemorrhage from minor to severe. Therefore, hemorrhage risk should be evaluated on a case-by-case basis.

VWD is diagnosed via the qualitative ristocetin cofactor assay (VWF:RCo) and the quantitative measurement of the amount of circulating von Willebrand's factor antigen (VWF:Ag) [18]. Type I and Type II VWD can be differentiated based on differences in ratios between the two assays, where a decrease in the VWF:RCo/VWF:Ag <0.6 is indicative of Type II VWD and a ratio VWF:RCo/VWF:Ag >0.6 is indicative of Type I VWD [17]. The PTT and bleeding time are often elevated in patients with VWD [19]. Management of Type I VWD includes the use of desmopressin, which results in a release of stored VWF. Due to inter-individual variability in response to desmopressin treatment, in patients with Type I VWD, a preliminary test dose to verify biological response to desmopressin is recommended [17]. Desmopressin is effective in most cases of Type I VWD, but is not used in Type II VWD or Type III VWD [20]. Type II VWD may actually be aggravated by the use of desmopressin. Specifically, in Type IIB VWD, there is a risk for the aggravation of thrombocytopenia [21]. The peak response to desmopressin

infusion occurs between 90 min and 2 h post-infusion, and therefore, surgery is recommended within 2 h post-infusion. Bornert et al. used a protocol of IV infusion (50 ml/30 min) of 0.2 µg/kg 1 h preoperatively, 10 h postoperatively, and 24 h postoperatively to obtain hemostasis in a pediatric patient with Type I VWD undergoing dental extractions [22]. This protocol can be used as a basic guideline for treatment of patients with Type I VWD undergoing dental extractions; alternatively, the use of 300 µg intranasal preoperatively in patients >50 kg, 150 µg intranasal in patients <50 kg, or subcutaneous 0.3 µg/kg max dose of 15 µg may also be considered [23–25]. The use of local hemostatic measures and antifibrinolytics is also recommended in the treatment of VWD. In cases of severe VWD, VWF/FVIII infusions have been used [17].

2.1.3. Hemophilias A and B

Hemophilias A and B are X-linked recessive bleeding disorders. Patients with hemophilia are unable to activate Factor X and therefore are unable to generate thrombin and fibrin necessary to stabilize the initial platelet plug. Hemophilia A is caused by a defect in Factor VIII and Hemophilia B, also known as Christmas disease, is caused by a defect in Factor IX. The incidence of Hemophilia A is approximately 1 in 5000, and the incidence of Hemophilia B is 1 in 30,000 [26]. Males are generally affected, whereas female carriers are generally asymptomatic, with some female carriers having symptoms similar-to-mild hemophilia [27]. While most cases of hemophilia have a family history of the bleeding disorder, approximately one-third of the cases arise spontaneously, with hemophilia occurring due to a de novo maternal mutation [28]. Hemophilias A and B can be further categorized based on the concentration of functional Factor VIII or IX. Severe hemophilia is identified as less than 1% of normal factor activity, moderate hemophilia 1–5% of normal factor activity, and mild hemophilia as 5–40% of normal factor activity [29, 30]. Two-thirds of patients with Hemophilia A have severe hemophilia, and one-half of patients with Hemophilia B have severe hemophilia. The average age of diagnosis of hemophilia for severe hemophilia is at 1 month of age, 8 months for moderate hemophilia, and 3 years for mild hemophilia. A family history of hemophilia or of mother carrier status increases the likelihood of diagnosis [31]. In mild hemophilia, the diagnosis may be challenging as diagnosis may only be made after a bleeding episode during surgery or trauma [32]. Symptoms in newborns include bleeding after circumcision and intracranial hemorrhage [33, 34]. Symptoms that present during early childhood include bruising, joint bleeds, and “goose-egg” hematomas of the forehead [35]. Symptoms that present later in childhood or during adult life include hemarthrosis and hematomas. Joints with frequent hemarthrosis are likely to develop arthropathy during adolescence [36]. In trauma patients with a history of hemophilia, there is an increased risk for life-threatening intracranial hemorrhage, which can present clinically as headache, vomiting, seizures, and lethargy [37]. In those patients with a family history of Hemophilia A, diagnosis can be made at birth by measuring Factor VIII levels on the umbilical cord blood [17]. In patients with a family history of Hemophilia B, diagnosis can be made between 6 and 12 months, as at birth Factor IX levels are low in all individuals [26]. Laboratory results in hemophilia indicate a prolonged PTT with normal PT and INR. A normal PTT does not exclude hemophilia due to a low sensitivity of the screening test. A prolonged PTT is then confirmed by identifying

decreased functional Factor VIII or IX at less than 40% of normal [17]. In patients with suspected Hemophilia A, a normal VWF:Ag should be present to rule out decreased Factor VIII as a result of von Willebrand Disease.

Once a diagnosis of hemophilia is made, patients should be vaccinated against Hepatitis B. At one year of age, vaccination against Hepatitis A can be administered to prevent viral transmission during the transfusion of blood products [38]. Management of hemophilia with acute bleeding can be achieved with factor replacement, fresh-frozen plasma (FFP), local measures, antifibrinolytic agents, and desmopressin in patients with Hemophilia A. Today, factor replacement is preferred to FFP due to relative concentrations of the products and decreased risk of transmission of blood borne pathogens. Long-term management of patients with hemophilia includes prophylactic treatment with factor replacement. Prophylaxis is achieved by maintaining the missing clotting factor at a level of 1% or higher. These protocols have resulted in a decrease in the chronic morbidities associated with hemophilia, such as arthropathy [39]. For factor replacement, one unit of Factor VIII per kg of body weight increases the plasma FVIII level by 2%. For Factor IX replacement, one unit of Factor IX per kg of body weight increases the plasma IX level by 1%. The half-life of Factor VIII is 8–12 h so twice-daily dosing is required. The half-life of Factor IX is 24 h so dosing is limited to once daily [40–42]. The control of serious bleeding is usually achieved by maintaining factors levels at 50–100% for a period of 7–10 days [43, 44]. Prophylaxis to prevent serious bleeding complications in patients with hemophilia includes achieving 100% factor function for a period of 1 week prior to surgery. Factor replacement is typically maintained postoperatively for 1–3 days [39]. Desmopressin can also be used in the management of Hemophilia A. Desmopressin at 0.3 µg/kg body weight is expected to raise FVIII levels by twofold within an hour post-infusion. This can be repeated after 12 h and once daily thereafter [45, 46]. Intranasal administration of 300 µg of desmopressin preoperatively in patients >50 kg, 150 µg intranasal in patients <50 kg, or subcutaneous 0.3 µg/kg max dose of 15 µg may also be considered [23–25]. Desmopressin is dependent on existing Factor VIII as it promotes the release of VWF, allowing for stabilization of Factor VIII. Therefore, desmopressin is ineffective in severe hemophilia (<1% activity) and in treating Hemophilia B [17].

Factor replacement therapy has its potential complications, such as the development of antibodies against the replaced factors. The development of inhibitors is reported to develop in 20% of severe cases of Hemophilia A and 3–5% of patients with Hemophilia B [47]. The development of inhibitor antibodies is diagnosed via mixing studies where the addition of the missing protein to the plasma of a subject with an inhibitor does not correct an abnormal PTT. The Bethesda assay is used to qualify patients with inhibitors into low responders or high responders. Low responders are patients with BU <5 and respond well to high doses of factor replacement. High responders, or patients with BU >10, do not respond well to factor replacement and are treated with concentrates of other factors including Factor VII to promote the intrinsic pathway of the coagulation cascade [48]. The future of hemophilia treatment likely includes the development of long-acting factor replacements and gene therapy [49]. In patients born before 1985, the leading cause of death in patients with hemophilia is complications from HIV or Hepatitis C due to contamination of the plasma supply [50, 51]. Today, the preferred

use of recombinant factors and improved methods in removing viruses from the donor blood supply has decreased the viral rate of transmission. Complications related to liver failure as a result of Hepatitis C further increases difficulties in managing the coagulopathy in these patients.

2.1.4. Hemophilia C

Factor XI deficiency or Hemophilia C is the fourth most common inherited bleeding disorder after VWD, Hemophilia A, and Hemophilia B. Hemophilia C is most common in the Ashkenazi Jewish population with 8% of this population being heterozygous [52, 53]. Unlike Hemophilias A and B, Factor XI deficiency is not defined by spontaneous bleeding into muscles and joints [52]. Hemophilia C can also be seen in both sexes, whereas Hemophilias A and B are inherited in an X-linked recessive manner and therefore are more common in males. Hemophilia C was first identified in two sisters, one of which had a tonsillectomy and the other a dental extraction [54]. Factor XI deficiency is most commonly identified after trauma or surgery to tissues with high fibrinolytic properties including the oral mucosa. Bleeding occurs more commonly in tissues with high fibrinolytic properties because the normal function of Factor XI is to stabilize thrombin-activated fibrinolysis inhibitor (TAFI), an inhibitor of fibrinolysis [55]. An elevated PTT is seen in patients with Hemophilia C with confirmation of Hemophilia C via measurement of Factor XI levels. Patients with $<20 \mu\text{dl}$ are identified as having a severe deficiency of Factor XI and patients with a Factor XI level of $20\text{--}80 \mu\text{dl}$ as having a partial deficiency [56]. The degree of Factor XI deficiency is poorly correlated with bleeding tendency for patients with partial deficiency. Overall, a history of bleeding episodes is more significant than the specific level of Factor XI [53]. In patients undergoing dental extractions, the use of tranexamic acid is an effective treatment. Berliner et al. reported no episodes of prolonged bleeding in patients with severe Factor XI deficiency $<15 \mu\text{dl}$ when tranexamic acid was used 12 h prior to procedure and continued for 7 days post-extraction [57]. In surgeries where more severe bleeding is expected the use of fresh-frozen plasma (FFP), 15 ml/kg within two days prior to surgery is an effective treatment modality [53]. Prior to transfusion with FFP, patients should be tested for Factor XI inhibitors [58]. If inhibitors are present, alternative treatment modalities should be explored including Factor VIIa. A single dose of Factor VIIa ($15\text{--}30 \mu\text{l/kg}$) in combination with tranexamic acid perioperatively has been effective in obtaining hemostasis in patients with Factor XI inhibitors [58]. Patients with severe Factor XI deficiency should be transfused with FFP to Factor XI levels of $30\text{--}40 \mu\text{dl}$, which can be identified via Factor XI testing or a normalized PTT [53]. Factor XI should not be normalized due to increased risk of thrombosis. Risks of FFP include fluid overload and those risks associated with blood products. Factor XI concentrate is another effective treatment modality, but due to the risk of thrombosis formation, Factor XI concentrate is not currently available in the United States [53].

2.1.5. Other inherited coagulopathies

Other rare forms of inherited coagulation disorders make up 3–5% of all coagulation disorders. These include deficiencies in fibrinogen, prothrombin, factor V, Factor V and VIII, VII, X, and XIII deficiency [17, 59–61]. These disorders can be screened for using PT, PTT, and INR assays.

If positive results are present, then a secondary diagnostic assay of factor activity can be performed [17]. Unique to the rare forms of inherited coagulopathies a normal PT, PTT, and INR with symptoms of CNS bleeding or hemarthrosis may indicate a Factor XIII deficiency [17, 62]. Treatment for these coagulopathies usually includes factor replacement [60].

2.3. Acquired disorders of hemostasis

2.3.1. Thrombocytopenia

There are various causes of thrombocytopenia including decreased platelet production, increased destruction, sequestration, dilution and consumption within clots. Some causes of thrombocytopenia are associated with hemorrhage, while others are associated with increased risk of thrombosis. Thrombocytopenia associated with increased risk of thrombosis includes heparin-induced thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and drug-induced thrombotic microangiopathy. Thrombocytopenia occurs in these disorders as platelets are consumed during the formation of clots. Thrombocytopenia in the presence of pancytopenia is indicative of a defect in the bone marrow including nutritional deficiencies, myelodysplastic syndromes, and acute leukemia. Additionally, drugs used to treat malignancies may cause pancytopenia. Isolated thrombocytopenia may be indicative of congenital thrombocytopenia, thrombocytopenia during pregnancy, autoimmune diseases, immune thrombocytopenia (ITP), drug-induced thrombocytopenia, or liver disease [63]. Patients who present with thrombocytopenia with a recent change in medications should be evaluated for drug-induced thrombocytopenia. The mechanism of thrombocytopenia in patients with liver disease is via spleen sequestration of platelets secondary to splenomegaly due to portal hypertension. Thrombocytopenia can be associated with infections viral, bacterial, or parasitic. Thrombocytopenia has been reported to be an initial presentation of HIV [64]. Patients with unexplained thrombocytopenia have a complex differential diagnosis and should be referred to a hematologist for consultation and complete workup. The average platelet count is 150,000–450,000/ μl representing great variability between individuals. While there is greater variability in platelet count between individuals, individuals typically have a consistent platelet level [65]. Therefore, a change in platelet count may be more indicative of an increased risk of hemorrhage compared to the platelet value itself. A platelet value below 150,000/ μl is defined as thrombocytopenia with severe thrombocytopenia being defined as a platelet count below 50,000/ μl . Severe thrombocytopenia may pose a risk for hemorrhage during surgical procedures, while spontaneous bleeding does not typically occur unless the platelet count is less than 10,000/ μl . Bleeding time should be evaluated in patients with thrombocytopenia. The bleeding time can be estimated by $\text{bleeding time} = 30.5 (\text{platelet count}/3850)$ [66]. Patients with thrombocytopenia should be transfused to a platelet count of 50,000/ μl prior to minor procedures and 100,000/ μl for more invasive procedures [66]. Patients should be transfused with platelets the morning of surgery due to the high rate of platelet consumption or sequestration. A platelet count should be taken post-transfusion. A history of prior transfusions is important to identify due to increased alloimmunization of the recipient against platelet products. Additional transfusions intraoperatively or postoperatively may be necessary. In addition to platelet transfusions,

local hemostatic measures including gelatin sponge, oxidized regenerated cellulose, topical thrombin, aminocaproic acid, and tranexamic acid should be used to obtain and maintain hemostasis. In patients undergoing dental extractions with a platelet count of $<100,000/\mu\text{l}$ and when $<50,000/\mu\text{l}$ were transfused with platelets, Fillmore et al. reported a 7.4% risk of postoperative bleeding, all of which were controlled via local measures [67].

2.3.2. Immune Thrombocytopenia

Immune thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura, is an immune-mediated thrombocytopenia in children, adults, or during pregnancy. ITP is a disease of exclusion with a differential diagnosis including thrombotic thrombocytopenic purpura (TTP), chronic liver disease, aplastic anemia, leukemia, Type IIB von Willebrand disease, drug-induced thrombocytopenia, myeloproliferative disorders, and HIV [68]. The presentation of ITP in children and adults differs, as in children ITP typically occurs after a viral infection and typically resolves spontaneously. ITP in adults is typically a chronic disease. ITP in adults is identified as either primary ITP or secondary ITP.

Primary ITP occurs suddenly with no apparent precipitating event. Secondary ITP occurs in patients with other morbidities including HIV, Hepatitis C, malignancies, or other autoimmune diseases. The cause of ITP is the production of IgG autoantibodies to platelet proteins, notably GPIIb/IIIa [69]. Once opsonized, platelets are destroyed by the reticuloendothelial system [68]. Clinical manifestations of ITP include bleeding consistent with a platelet defect. Symptoms include petechiae, purpura, epistaxis, and most severely intracranial hemorrhage. Intraoral blisters or bleeding known as “wet purpura” has historically been identified as a more concerning presentation than petechiae or purpura of the skin [70]. Typically, spontaneous bleeding does not occur in patients with platelet counts greater than 30,000/ml, and patients with a platelet count greater than 30,000/ml have mortality risks equal to the general population [71, 72]. Patients with ITP typically have less bleeding risk than would be anticipated by the reduced platelet count. This is likely related to the majority of platelets being younger with greater hemostatic activity, as the autoimmune nature of ITP results in a shortened platelet life span [73, 74]. Patients do not need to be treated for ITP unless platelet counts are $<10,000/\text{ml}$, there is the presence of spontaneous bleeding, patients are scheduled for surgery, or patients have lifestyles or occupational demands that increase the risk for trauma [73]. The presence of comorbidities including chronic liver disease, hypertension, infection, and uremia-induced platelet dysfunction is another factor that should be considered when deciding to treat patients with ITP [73]. Recommendations for safe practice in patients undergoing surgical procedures are platelet count $>30,000/\text{ml}$ for a single simple extraction, $>50,000/\text{ml}$ for minor surgery, and $>80,000/\text{ml}$ for major surgery [68]. Typical first-line therapy in consultation with a hematologist includes prednisolone at 1 mg/kg for 2–4 weeks, followed by tapering over several weeks. If corticosteroids are unsuccessful or not indicated, IVIG 1 g/kg for 2 days or anti-D 50 $\mu\text{g}/\text{kg}$ once can be used. For patients who fail first-line therapy, second-line therapy includes splenectomy, followed by additional pharmacotherapy [73]. In the patient with ITP necessitating emergency surgery, a protocol including IVIG and platelet transfusions is used [73–76].

2.3.3. Liver disease

Common causes of chronic liver disease include viral hepatitis and alcoholic liver disease. Candidates for liver transplantation due to liver cirrhosis are required to have dental clearance as part of a preoperative evaluation prior to being placed on the transplant list. This often includes extraction of carious dentition that is deemed to be an infection risk. The liver plays a crucial role in hemostasis as the liver is the site of synthesis of thrombopoietin, most of the coagulation factors, the inhibitors of the coagulation cascade and fibrinolytic proteins. In addition to the site of synthesis, the liver is the site of metabolism of these factors. Due to diminished procoagulant and anticoagulant factors, there is a rebalancing of hemostasis, and most patients with liver disease undergoing surgical procedures do not exhibit excessive bleeding [77]. Additionally, von Willebrand's factor (VWF) is not produced in the liver and is elevated in patients with chronic liver disease. Increased VWF may contribute to maintenance of primary hemostasis [78]. Patients with liver disease should be treated with caution, as the balance between procoagulant and anticoagulant factors can easily be disrupted resulting in either a hypercoagulable or hypocoagulable state. PT, INR, and PTT are commonly prolonged in patients with liver failure, but this does not necessarily indicate an increased bleeding risk as PT and PTT are unable to account for the decreased production of the anticoagulant factors protein C, S, and antithrombin [77]. Prophylactic correction of prolonged PT with fresh-frozen plasma is not recommended prior to procedures due to limited reduction in bleeding risk and the risks of blood products [79]. Additionally, volume overloading can increase the possibility of varices rupturing as a consequence of portal hypertension [80]. Patients with liver disease commonly present with moderate thrombocytopenia (50,000–100,000/ μ l) due to a decreased production of thrombopoietin in the liver, as well as platelet sequestration in the spleen due to portal hypertension [81]. For platelet count $>50,000/\mu$ l, there is limited risk for significant bleeding. For patients with a platelet count $<50,000/\mu$ l, platelets should be transfused to $>50,000/\mu$ l. The use of antifibrinolytic agents such as tranexamic acid oral rinse preoperatively is indicated to prevent bleeding complications. Stanca et al. successfully used intranasal desmopressin (300 μ g) in patients with INR of 2–3 and platelet count $<50,000/\mu$ l prior to dental extractions to promote hemostasis [82]. Additionally, platelet and coagulation factor deficiencies may occur in alcoholics due to nutritional deficiencies in folic acid and vitamin K associated with poor diets. Correction of folic acid and vitamin K (10 mg orally for 3 days) prior to surgical intervention may be indicated. For pain management, NSAIDs should be avoided in patients with liver disease due increased bleeding risk. Comorbidities that may increase bleeding risk including current infection, uremia that impairs degranulation of platelets, and medications that may affect coagulation. Infections should be treated and renal status optimized prior to surgical intervention [77]. As liver disease does not prevent against thrombosis, prior to surgery, anticoagulant therapy should not be suspended solely based on liver disease status [83].

2.3.4. Renal Dysfunction

In patients with renal dysfunction, there is an increased susceptibility to bleeding. This increased bleeding risk is multifactorial and includes platelet dysfunction due to uremia,

platelet dysfunction due to anemia, and the anticoagulant effects of heparin used during dialysis. Platelet dysfunction due to uremia can affect all stages of platelet function including adhesion, secretion, and aggregation [84]. This includes an increase in prostacyclin and nitric oxide levels, decreased production of thromboxane A₂, abnormal intracellular calcium mobilization, and decreased production of ADP, epinephrine, and serotonin [85–88]. Well-characterized effects of uremia on platelet function include intrinsic platelet dysfunction in GPIIb/IIIa resulting in decreased platelet aggregation and adhesion [89]. Uremia can also induce platelet dysfunction extrinsic to platelets via the production of inhibitors including guanidinosuccinic acid that increase nitric oxide levels [90]. Nitric oxide is a potent inhibitor of platelet aggregation.

Anemia occurs in patients with renal dysfunction due to a decrease in erythropoietin. In a patient with a normal hematocrit, red blood cells occupy the center of the blood vessel, while the platelets are located at the periphery of the blood vessel. The peripheral location of platelets in the blood vessel allows platelets to easily contact the subendothelial collagen when the endothelium is damaged. In patients with anemia, the platelets are mixed with the red blood cells and are less able to contact damaged endothelium [84].

Nishide et al. published a case report of increased hemorrhage in a patient with renal dysfunction undergoing full mouth dental extractions and removal of hyperplastic gingiva two months prior to kidney transplantation [91]. The authors noted no abnormalities in PT, PTT, or bleeding time on preoperative laboratory tests. Abnormal laboratory results included decreased hemoglobin of 7.2 g/dl and an elevated creatinine of 8.9 mg/dl consistent with renal failure. In patients undergoing dialysis treatment, it is recommended that patients undergo surgical procedures the day after dialysis when the anticoagulant effects of heparin have subsided. To limit the negative effects of anemia on hemostasis, it is recommended to transfuse patients to a hemoglobin of 10 g/dl preoperatively [92]. Additional strategies to promote hemostasis preoperatively include the use of desmopressin single dose IV 0.3 µg/kg or 300 µg intranasally 2 h prior to procedure [93]. The use of desmopressin increases the release of vWF, therefore increasing the binding of platelets to subendothelial collagen in the damaged endothelium. Estrogen 0.6 mg/kg IV or 2.5–25 mg orally beginning 5 days preoperatively can also be used [94]. Estrogen promotes platelet function by limiting the production of nitric oxide [95]. Additionally, the use of local hemostatic measures is recommended. Patients with chronic renal failure may be at an increased risk of bleeding due to the presence of comorbidities such as cardiovascular disease that are managed with antiplatelet therapy or vitamin K antagonists [96, 97]. Patients with uremia should avoid NSAIDs as analgesics, as there is an increased risk of bleeding.

3. Iatrogenically induced coagulopathies

3.1. Vitamin K antagonists (Warfarin)

Warfarin is a commonly used anticoagulant in patients with atrial fibrillation, history of pulmonary embolism, possibility of deep vein thrombosis, and in patients with prosthetic

heart valves. Warfarin management can be challenging based on the narrow therapeutic range and other variables, such as drug interactions, diet, and systemic illnesses. Warfarin functions by inhibiting the enzyme epoxide reductase, which reduces vitamin K from its oxidized form so that it may participate in the carboxylation and activation of glutamate residues on coagulation factors II, VII, IX, X, protein C, and protein S.

Protein C and protein S are endogenous anticoagulant proteins and have shorter half-lives than factors II, VII, IX, and X [98]. Therefore, the initial effect of warfarin is a hypercoagulable state, with the anticoagulant effects of warfarin occurring after 2–3 days [99]. Due to the initial hypercoagulable state, patients at a high risk for a thromboembolic event may undergo bridging therapy with heparin for a period of 5–7 days. The effects of warfarin can be evaluated via PT or INR testing. Warfarin has an oral bioavailability of 100%, and over 99% of warfarin is bound to albumin. Due to the high protein binding of warfarin, the presence of other highly protein bound drugs may lead to the displacement of protein bound warfarin resulting in an increase in anticoagulation. Medications that promote the effects of warfarin include broad-spectrum antibiotics, fluconazole, metronidazole, erythromycin, cimetidine, phenytoin, and propranolol [98]. Additionally, broad-spectrum antibiotics may disrupt the normal gut flora, resulting in a decrease in vitamin K absorption and an increase in the effect of warfarin [100]. Medications that antagonize the effects of warfarin include steroids, cholestyramine, griseofulvin, rifampin, barbiturates, and carbamazepine [98]. There is also great inter-individual variation in dose to achieve therapeutic anticoagulation due to genetic variation in the cytochrome p450 enzymes, further necessitating the need for regular INR monitoring. Despite genetic variation in p450 enzymes, genetic testing prior to initiation of warfarin therapy is not recommended, as there is limited evidence to support reduced risk of bleeding or thromboembolism with altered initial dosage; 5.0 mg once per day is the standard initial dosage for patients initiating warfarin, as higher dosages have been associated with increased bleeding events [101, 102]. In elderly patients or patients at increased sensitivity to warfarin, a lower initial dose of 2.5 mg per day may be indicated [103]. In patients with thrombotic disease, the INR is usually titrated to 2.0–3.0 and in patients with valvular disease it is titrated from 2.5 to 3.5.

Due to balancing the risk of hemorrhage while on warfarin and the increased risk for thromboembolism in patients whose anticoagulation is discontinued, Ward and Smith determined there remains a disparity in perioperative management of patients on warfarin undergoing dentoalveolar procedures [104]. In most clinical situation, the trend is to limit modifications to warfarin therapy and promote hemostasis with use of local hemostatic agents. In a randomized controlled trial comparing maintenance of warfarin therapy to bridging with low molecular weight heparin (LMWH), Bajkin et al. determined there was no statistical difference in post-extraction bleeding between the two groups when local hemostatic measures were used. The authors concluded that in patients on warfarin with an INR of less than or equal to 4, simple dental extractions could safely be performed without modification to the patient's oral anticoagulant therapy [105]. Morimoto et al. determined that patients on antiplatelet therapy and anticoagulant therapy with INR <3.0 can safely undergo dental extractions without risk of excessive bleeding [106]. Cocero et al. determined in patients with comorbid-

ities such as diabetes, liver disease, and kidney failure that the INR safety window should be adjusted to <2.3 [107].

In patients undergoing surgical procedures with a higher risk of bleeding including head and neck surgery and reconstructive plastic surgery, warfarin should be stopped 5 days preoperatively [108]. The use of bridging anticoagulation with unfractionated heparin or low molecular weight heparin should be based on the thromboembolic risk of the patient. The American College of Chest Physicians (ACCP) as part of the Perioperative Management of Antithrombotic Therapy of the Antithrombotic Therapy and Prevention of Thrombosis 9th ed. has developed a three-tiered thromboembolic risk stratification of patients with mechanical heart valves, atrial fibrillation, and history of venous thromboembolism [108]. The risk stratification includes high risk ($>10\%$ /years of ATE or $>10\%$ /months of venous thromboembolic events (VTE)), intermediate risk ($4\text{--}10\%$ /years risk of ATE or $4\text{--}10\%$ /months risk of VTE), and low risk ($<4\%$ /years risk of ATE or $<2\%$ /months risk of VTE). In patients at a high risk for thromboembolism bridging anticoagulation is recommended [102]. In patients at low risk for thromboembolism, bridging anticoagulation is not recommended [102]. In patients at moderate risk for thromboembolism, use of bridging anticoagulation should be determined on a case-by-case basis [108]. In cases of excessive anticoagulation, the effects of warfarin can be stopped by the administration of parenteral vitamin K, prothrombin complex concentrate (PCC), or fresh-frozen plasma; 4 factor PCC including factors II, VII, IX, and X are preferred over FFP based on an increased rate of INR correction with fewer side effects [109].

3.2. Heparin and derivatives

3.2.1. Heparin (HMWH, unfractionated heparin)

Heparin is an endogenously produced linear polysaccharide with anticoagulant effects [110]. Heparin binds to antithrombin, formerly known as antithrombin III, increasing the anticoagulant effect of antithrombin by a factor of 1000. The binding of heparin to antithrombin results in a conformational change allowing for increased binding to clotting factors. Antithrombin activation leads to the inactivation of thrombin, Factor IX, and Factor X [104]. HMWH is unique compared to low molecular weight heparin and fondaparinux due to its ability to inhibit thrombin. HMWH is able to inhibit thrombin by the formation of a complex between HMWH, antithrombin, and thrombin that requires the long chains found in HMWH [111]. The molecular weight HMWH is 5000–30,000. In patients on HMWH, close monitoring via PTT is necessary. The therapeutic levels of heparin are typically 1.5–2.5 normal PTT [112]. Typically, the therapeutic range is 0.3–0.07 units/ml (anti-Xa units), which is achieved via a bolus of 80–100 units/kg, followed by 15–20 units/kg/h [113]. The onset of parenteral HMWH is nearly immediate with a half-life of 45 min to 1 h [114]. Low-dose prophylaxis can be achieved with 5000 units subcutaneously every 8–12 h. Peak plasma concentration of subcutaneous heparin occurs at 2–4 h post-administration. In patients on bridging anticoagulation with heparin, it is recommended that patients have HMWH discontinued 4–6 h prior to surgery with postoperative resumption of HMWH after hemostasis has been achieved [108]. In surgeries with a high risk of bleeding, resumption of HMWH is done after 48–72 h [108]. The most common serious

side effect of heparin treatment is heparin-induced thrombocytopenia (HIT). HIT is a hypercoagulable state that occurs in 1–4% of patients receiving unfractionated heparin due to antibodies to platelet factor 4 and heparin [115]. The formation of a thrombus or sudden decrease in platelet levels should raise suspicion for HIT. HMWH is metabolized by the liver and is unaffected by renal function. Reversal of the anticoagulant effect of heparin is achieved with the antagonist protamine. Protamine binds avidly to heparin reducing its anticoagulant effect. For every 100 units of heparin remaining in the patient, 1 mg of protamine is administered. Protamine should be administered slowly at a maximum rate of 20 mg/min (not to exceed 50 mg in a 10-min period).

3.2.2. Low molecular weight heparin (enoxaparin, dalteparin, and tinzaparin)

Low molecular weight heparin (LMWH) is derived from HMWH to produce a polysaccharide with a molecular weight of 2000–9000 Da [116]. LMWH, like heparin, leads to anticoagulation by promoting antithrombin to inactive Factor X and II. LMWH has a greater effect on Factor X compared to its effect on thrombin [98]. Advantages of LMWH over heparin include less frequent dosing and more predictable anticoagulant response compared to HMWH, limiting the need for laboratory monitoring. LMWH is unable to cross the placenta and is therefore the ideal anticoagulant during pregnancy. Disadvantages of LMWH include delayed onset, decreased effectiveness of protamine as a reversal agent, limitations in patients with renal failure and inability to monitor by PTT [117]. For enoxaparin, full-dose therapeutic levels should be titrated to 0.5–1.0 units/ml antifactor Xa for twice-daily dosing or 1.5 units/ml for once-daily dosing. Antifactor Xa should be used to measure activity of LMWH when indicated. For enoxaparin, prophylaxis 30 mg twice daily or 40 mg once daily should be given subcutaneously. Prophylactic dalteparin is typically administered as 5000 units every 8–12 h. Plasma concentrations peak at 2 h for IV administered LMWH and after 3–5 h for subcutaneously administered LMWH. The half-life is approximately 2 h. In patients receiving therapeutic subcutaneous LMWH as part of bridging anticoagulation, it is recommended that LMWH be discontinued 24 h prior to surgery and continued 24 h post-surgery pending hemostasis. In higher bleeding risk surgeries, LMWH should be continued 48–72 h post-surgery [108]. Protamine may be used to reverse the effects of LMWH. For LMWH administered in the last 8 h, 1 mg of protamine should be administered for every 1 mg of LMWH. For administration of LMWH longer than 8 h, prior 0.5 mg of protamine should be administered for every 1 mg of LMWH [118].

3.2.3. Fondaparinux (Arixtra)

Fondaparinux (Arixtra; GlaxoSmithKline, Mississauga, Ontario) is a small synthetic pentasaccharide fragment of heparin with a molecular weight of 1700 Da. Fondaparinux is an inhibitor of Factor Xa with high affinity for antithrombin compared to HMWH [98]. Fondaparinux is approved for prophylaxis of venous thromboembolic events (VTE) for up to one-month post-orthopedic surgery of the lower limbs, prophylaxis of VTE for patients undergoing abdominal surgery with high risk of thromboembolic events and in the acute treatment of DVT and pulmonary embolism [119]. Fondaparinux is not currently used for

long-term anticoagulation therapy. For prophylaxis, 2.5 mg of fondaparinux is administered subcutaneously once daily beginning 6–12 h post-surgery [120]. For VTE therapy, 5–10 mg is administered subcutaneously once daily in a weight-dependent manner. The half-life of fondaparinux is 17–21 h in patients with good renal function. The excretion of fondaparinux is highly dependent on renal function as 77% of fondaparinux is excreted unchanged in the urine within 72 h post-administration in patients with good renal function under the age of 75 years [119]. In patients with moderate renal insufficiency, creatinine clearance 30–50 ml/min, the half-life of fondaparinux is 29 h, and in patients with severe renal insufficiency, creatinine clearance <30 ml/min, the half-life of fondaparinux is 72 h [119]. Due to its renal excretion and concerns of prolonged bleeding, fondaparinux is contraindicated in patients with severe renal insufficiency. Fondaparinux has advantages over traditional heparin in terms of a reduced risk for heparin-induced thrombocytopenia. Fondaparinux is not currently approved for the use of “bridging,” and there are currently no randomized controlled trials with fondaparinux used as a bridging therapy. There are limited case studies with fondaparinux used as bridging therapy, with Wei et al. publishing a case report in a patient with a history of HIT requiring perioperative bridging due to mitral valve replacement prior to resection of esophageal squamous cell carcinoma. The patient was successfully bridged using 2.5 mg of fondaparinux subcutaneously, with the last dose of fondaparinux given 30 h preoperatively and resumed 24 h postoperatively [121]. In patients with HIT or antithrombin deficiency, where heparins are contraindicated, the use of fondaparinux for perioperative bridging may be indicated but further investigation is required. Initial recommendations for discontinuation of fondaparinux preoperatively would be 3–5 half-lives, similar to other anticoagulants. This recommendation is based solely on expert opinion, with no differentiation between the 2.5 mg prophylaxis dose and 5–10 mg therapeutic dose [122]. In patients with good renal function, this would be at least 2 days prior to a surgical procedure with minimal bleeding risk and 4 days prior to a surgical procedure with a high risk of bleeding. In patients with mild-to-moderate renal dysfunction, these time points should be adjusted accordingly [122].

3.3. Antiplatelet Therapy

3.3.1. Aspirin

Aspirin is used in the prophylactic treatment of myocardial infarction, stroke, and acutely in acute coronary syndrome. For prophylaxis, patients regularly take 75–100 mg/day indefinitely [123] with 81 mg being the most common dose in the United States. Aspirin's mechanism of action is the irreversible inhibition of cyclooxygenase-1 (COX-1). By inhibition of COX-1, there is a decrease in formation of thromboxane A₂ in platelets and therefore a decrease in platelet aggregation [56]. As aspirin is an irreversible inhibitor of COX-1, its effect is for the life span of the platelet. For dentoalveolar surgery, rarely is discontinuation of aspirin recommended. This is supported in the literature by Medeiros et al. who determined no difference in the amount of bleeding that occurred during tooth extraction between patients who continued prophylactic doses of aspirin therapy compared to those who suspended aspirin therapy [124]. In patients who are undergoing procedures with a high risk of bleeding including head and

neck surgery and reconstructive plastic surgery, cessation of aspirin should be based on the cardiovascular risk of the patient. In patients with a high risk for a cardiovascular event, aspirin therapy should be continued perioperatively, and in patients with a low risk of a cardiovascular event, aspirin therapy should be discontinued 7–10 days prior to surgery [108]. Patients at high risk for a cardiovascular event include those patients with congestive heart failure, diabetes mellitus, renal insufficiency, ischemic heart disease, and cerebrovascular disease [108].

3.3.2. P2Y₁₂ receptor blockers

The P2Y₁₂ blockers receptor blockers include clopidogrel, ticlopidine, prasugrel, ticagrelor, and cangrelor. The P2Y₁₂ blockers function by blocking the binding of ADP to the P2Y₁₂ receptor on platelets, resulting in an inhibition of platelet aggregation [125]. Clopidogrel, ticlopidine, and prasugrel are irreversible inhibitors of P2Y₁₂ via prodrug conversion to active metabolites, while ticagrelor and cangrelor are direct reversible inhibitors of P2Y₁₂. As a result of being irreversible inhibitors, there is a slower offset of action of clopidogrel, ticlopidine, and prasugrel compared to the reversible inhibitors [126]. Clopidogrel is the prototypical P2Y₁₂ receptor blocker, but it is not an ideal anticoagulant due to its slow onset of action due to being a prodrug, unpredictable pharmacodynamics due to its p450 interactions, and slow offset as an irreversible inhibitor. Ticlopidine use is limited due its side effect of severe neutropenia. Prasugrel and ticagrelor have come into favor due to increased prevention of cardiovascular events [127, 128]. Prasugrel and ticagrelor also carry a high risk of bleeding compared to clopidogrel due to their faster onset and more consistent platelet inhibition [126]. P2Y₁₂ blockers are commonly used along with aspirin for dual-antiplatelet therapy in patients with NSTEMI or coronary stent placement [129]. The current recommendation for patients with drug eluding stents is at least 12 months of dual-antiplatelet therapy, followed by an additional 18 months of dual-antiplatelet therapy considering the increased risk for bleeding [130]. The recommendations for bare metal stents are the same as for drug eluding stents with improved outcomes at greater than 12-month dual-antiplatelet therapy [131]. In patients undergoing dental extractions, Bajkin et al. determined that there was no increased risk in postoperative bleeding in patients on dual-antiplatelet therapy with clopidogrel and aspirin compared to patients on no antiplatelet therapy [132].

3.4. Direct oral anticoagulants (DOACs)

Direct oral anticoagulants (DOACs) including thrombin and Factor X inhibitors are being used in treatment of stroke prevention in patients with atrial fibrillation, prophylaxis for venous thromboembolism post-surgery, in management of venous thromboembolism, in secondary prevention of thromboembolism, and in heparin-induced thrombocytopenia. DOACs are contraindicated in patients with prosthetic heart valves, severe renal impairment, and during pregnancy. Compared to warfarin, the DOACs have several advantages. This includes a rapid onset of action, a relatively wide therapeutic range, and a decrease in need for regular coagulation monitoring. Compared to heparin, DOACs have the advantage of oral bioavailability. Direct factor inhibitors are also reported have an overall lower bleeding risk compared

to warfarin [133]. With a decreased necessity for close monitoring, there is an increased concern for patient compliance. While compliance between patients taking vitamin K antagonists and DOACs may be equal, missing a single dose of a DOAC has an increased risk of anticoagulation outside the therapeutic window compared to missing a single dose of warfarin [134]. Other concerns include a current lack of specific antidotes. Direct thrombin inhibitors include parenteral bivalirudin (Angiomax; The Medicines Company Parsippany, NJ, USA), argatroban, and desirudin. Bivalirudin is a synthetic analog to hirudin, a natural anticoagulant in the saliva of leeches. Bivalirudin is renally excreted and in patients with adequate renal function has a half-life of 25 min. Similar to other DOACs, there is no antidote for bivalirudin. Bivalirudin has been used as an alternative to heparin in patients with HIT [135, 136]. The only oral direct thrombin inhibitor is dabigatran (Pradaxa; Boehringer Ingelheim Ridgefield, CT, USA). There are no parenteral Factor X inhibitors. Oral Factor X inhibitors include rivaroxaban (Xarelto; Janssen Pharmaceutica, Belgium), apixaban (Eliquis; Bristol-Myers Squibb, New York, NY, USA), and edoxaban (Lixiana; Daiichi-Sankyo, Japan).

3.4.1. Dabigatran (Pradaxa)

Dabigatran is a competitive direct thrombin inhibitor. Thrombin is the final enzyme of the coagulation cascade that cleaves fibrinogen into fibrin. In addition, thrombin also activates factors V, VIII, XI, and XIII [137]. Dabigatran is able to block the action of both circulating and clot bound thrombin therefore preventing the propagation of clots. This is unique from heparin, which only blocks circulating thrombin [138]. Dabigatran is approved to reduce the risk of stroke in atrial fibrillation, treatment of venous thromboembolism, and secondary prevention of venous thromboembolism with a dosing of 150 mg twice a day in patients with good renal function. In post-surgical patients for prevention of venous thromboembolism, 110 mg is administered post-surgery followed by 220 mg once daily for one to four weeks. The prodrug dabigatran etexilate has a 6–7% oral bioavailability [139, 140]. Peak plasma concentration is achieved in 1–2 h and the half-life ranges from 12 to 17 h [141]. The anticoagulant effects of dabigatran last for 2–3 days. The drug is cleared renally and should be avoided in patients with severe renal impairment [142]. Dabigatran has fewer drug interactions than warfarin as it is not metabolized by the p450 system, but should be avoided in patients taking amiodarone, verapamil, quinidine, and rifampin as these drugs increase the effects of dabigatran [139, 140]. The antidote for dabigatran is idarucizumab (Praxbind Boehringer Ingelheim, Germany), a monoclonal antibody that can be used in emergency situations for reversal of dabigatran [143]. In the RE-LY trial, Eikelboom et al. determined that there was no increased risk of bleeding with warfarin titrated to an INR of 2–3 compared to dabigatran 150 mg twice a day [144]. There are currently no randomized controlled trials evaluating the risk of bleeding in patients on dabigatran undergoing dental extractions. The limited evidence in managing patients undergoing dental extractions indicates continuing anticoagulant treatment, delaying extractions as long as possible since the last dosage of dabigatran, and the use of local hemostatic agents [145]. If dabigatran is to be interrupted preoperatively, renal function should be considered. In patients with normal or mild impairment of renal function undergoing surgery with low bleeding risk, the last dose should be administered 2 days before surgery, and in patients with moderate renal impairment, the last dose should be administered 3 days before

surgery. In patients with normal or mild impairment of renal function undergoing surgery with a high bleeding risk, the last dose should be administered 3 days before surgery, and in patients with moderate renal impairment, the last dose should be administered 4–5 days before surgery [146]. In emergency situations, the safe concentration for dabigatran at which surgery can be performed without the risk of major bleeding is less than 30 ng/ml. A PTT and PT ratio of <1.2 compared to normal is indicative of a dabigatran concentration of <30 ng/ml. If PTT and PT concentration is greater than 1.2 compared to normal, treatment should be delayed for 24 h and new laboratory tests taken prior to treatment [147].

3.4.2. Rivaroxaban (*Xarelto*)

Rivaroxaban is a competitive direct Factor X inhibitor. Activated Factor X cleaves prothrombin to thrombin. Rivaroxaban is able to bind to both circulating and clot bound Factor X, preventing the propagation of clot formation. This is unique from heparin, which only binds to circulating Factor X. Rivaroxaban is approved for prevention of stroke in patients with atrial fibrillation, prevention of venous thromboembolism following surgery, and in the treatment and prevention of venous thromboembolism [108]. There is no prodrug for rivaroxaban. For post-surgical prophylaxis of VTE, 10 mg is used daily for 2–5 weeks; for treatment and prevention of VTE, 15 mg is given twice daily for 3 weeks followed by 20 mg once daily; for stroke prevention in atrial fibrillation, 20 mg is used once daily in patients with good renal function. The oral bioavailability is ~80%. Peak plasma concentration is achieved in 2.5–4 h [108, 109]. Rivaroxaban has a half-life of 5–9 h, and the anticoagulant effect lasts for 1–2 days [110]. One-third is excreted renally, and two-thirds are converted by CYP 3A4 to inactive metabolites. Therefore, strong p450 inhibitors and inducers may have significant drug interactions [148]. Rivaroxaban is not recommended in patients with poor renal function or poor liver function [149]. There is no known antidote for rivaroxaban. There are currently no randomized controlled trials evaluating the risk of bleeding in patients on rivaroxaban undergoing dental extractions. As part of the ROCKET AF Trial, Sherwood et al. determined that there was a higher risk of major and minor GI bleeding compared to warfarin, but no difference in severe bleeding [150]. The limited evidence in managing patients undergoing dental extractions indicates continuing anticoagulant treatment, delaying extractions as long as possible since the last dosage of rivaroxaban, and the use of local hemostatic agents. If rivaroxaban is to be interrupted preoperatively, renal function should be considered. For patients with normal, mild, or moderate impairment of renal function undergoing surgery with a low bleeding risk, the last dose should be given 2 days prior to surgery, for a surgery with a high bleeding risk the last dose should be given 3 days before surgery. For patients with severe impairment of renal function, creatinine clearance less than 30 ml/min, undergoing surgery with a low bleeding risk the last dose should be given 3 days before surgery and for a surgery with a high bleeding risk the last dose should be given 4 days before surgery [106]. The concentration for rivaroxaban at which emergency surgery can be performed without major risk of bleeding is less than 30 ng/ml. Regular laboratory testing of rivaroxaban concentration is not always available, but analysis of PT and PTT can act as a good indicator. A PTT and PT ratio of <1.2 compared to normal is indicative of a rivaroxaban concentration of <30 ng/ml. If PTT and PT concentration

is greater than 1.2 compared to normal, treatment should be delayed for 24 h and new laboratory tests taken prior to treatment [107].

3.4.3. Apixaban (*Eliquis*)

Apixaban is a direct oral Factor X inhibitor. The half-life of apixaban is 5–9 h [101]. Apixaban can be used in post-surgical VTE prophylaxis, treatment and prevention of VTE, and stroke prevention patients with atrial fibrillation. Compared to other DOACs, apixaban has the least risk for bleeding complications [151]. There are currently no randomized controlled trials evaluating the risk of bleeding in patients on apixaban undergoing dental extractions. The limited evidence in managing patients undergoing dental extractions indicates continuing anticoagulant treatment, delaying extractions as long as possible (since the last dosage of apixaban) and the use of local hemostatic agents. If apixaban is to be interrupted preoperatively, renal function should be considered. In patients with normal or mild impairment of renal function undergoing surgery with low bleeding risk, the last dose should be administered 2 days before surgery, and in patients with moderate renal impairment, the last dose should be administered 3 days before surgery. In patients with normal or mild impairment of renal function undergoing surgery with a high bleeding risk, the last dose should be administered 3 days before surgery, and in patients with moderate renal impairment, the last dose should be administered 4 before surgery [106].

4. Local hemostatic agents

In many patients, local hemostatic agents are an efficient and cost-effective way to limit blood loss. By limiting blood loss in the perioperative period, there is a decreased need for additional interventions and their associated morbidities, including blood transfusions and their associated risks. The use of local hemostatic agents aids in preventing the need for the discontinuation of anticoagulant therapy that would place patients at risk of thromboembolic events. Additionally, the use of local hemostatic agents is cost-effective by decreasing the need for follow-up due to incidence of “rebleeding.” Local hemostatic agents can be divided into two main categories: physical agents that provide scaffolding for clot formation and biologically active agents that include clotting factors or antifibrinolytics that promote clot formation or inhibit clot dissolution. Physical agents include bone wax, oxidized regenerated cellulose (Surgicel; Ethicon, Neuchatel, Switzerland), and gelatin matrix (Gelfoam; Pfizer, New York, NY, USA). Biologically active agents include topical thrombin (RECOTHROM; Zymogenetics, Seattle, WA, USA), aminocaproic acid (AMICAR; Clover Pharmaceuticals, Marietta, GA, USA), and tranexamic acid (IV Cyklokapron; Pfizer, New York, NY, USA) (oral tablet LYS-TEDA; Ferring Pharmaceuticals Saint-Prex-Switzerland).

Oxidized regenerated cellulose (Surgicel) is a resorbable sterile mesh that can be layered at a bleeding surgical site. Surgicel has bactericidal properties due to its acidic pH [152]. This is an advantage of Surgicel over other hemostatic agents, as the highly absorptive properties of other physical hemostatic agents at a neutral pH have been shown to be a nidus for infection. The

acidic pH of Surgicel may have a negative effect on other hemostatic agents, such as thrombin. Surgicel is known to inhibit topical thrombin; thus, Surgicel and topical thrombin should not be used together to promote hemostasis. Additionally, Alkan et al. and Loescher and Robinson in two separate animal models have determined that Surgicel when placed in close proximity to nerves may have a negative effect on peripheral nerve function [153, 154].

Gelfoam is a highly absorbable gelatin matrix prepared from purified porcine. Gelfoam is highly pliable, can easily be placed in bleeding extraction sockets, and completely reabsorbs in 4–6 weeks [155]. The main effect of Gelfoam is to act as a scaffold for coagulation. Gelfoam has a neutral pH. The use of Gelfoam as a physical matrix combined with topical thrombin as a biological agent is an effective way to obtain hemostasis. The highly absorptive property of Gelfoam has been reported to act as a nidus for infection and granuloma formation.

HemCon Dental Dressing (Zimmer Holdings, HemCon Medical Technologies Inc., Beaverton, OR, USA) is an absorbable chitosan derived dressing used for hemostasis in dental extraction sites [156]. Advantages of HemCon include its antimicrobial properties and its ability to be placed over extraction sockets compared to being placed in extraction sockets and sutured in place [157]. CollaPlug (Zimmer Dental, Carlsbad, CA, USA) is an absorbable collagen based agent that acts a physical matrix to promote the coagulation cascade in extraction sockets. The absorbable collagen membrane is also marketed as CollaTape for closure of graft sites and repair of Schneiderian membrane tears, as well as CollaCote to be placed over soft-tissue donor sites [158]. In a recent study, Pippi et al. compared HemCon to CollaPlug and found favorable outcomes in patients on anticoagulant therapy undergoing dental extractions with INR less than 3.5 with both hemostatic agents. The authors reported advantages of HemCon, such as reduced operative time and improved soft-tissue healing, which they attributed to obviating the need for suturing [156].

Bone wax, a mixture of beeswax and isopropyl palmitate, is an inexpensive and effective way of occluding small bleeding vessels in bone. Bone wax does not act as a scaffold for coagulation or contain coagulation factors, but rather a compressive and occlusive dressing. Increased risk of infection is reported with the use of bone wax [159].

Topical thrombin is able to convert fibrinogen to fibrin in the final step of the coagulation cascade. Topical thrombin is available in a liquid form and can be an effective way to obtain hemostasis when combined with Gelfoam or collagen matrices. As mentioned previously, Surgicel and thrombin should not be used together.

Tranexamic acid and aminocaproic acid are antifibrinolytic agents composed of synthetic lysine residues capable of blocking plasminogen and plasmin binding to fibrin. Tranexamic acid can be administered intravenously or topically. In patients undergoing orthognathic surgery, Choi et al. determined that a bolus of tranexamic acid (20 mg/kg) preoperatively significantly reduced intraoperative bleeding compared to controls [160]. In a recently published randomized control trial, Eftekharian et al. used tranexamic acid (1 mg/mL) in combination with normal saline as an irrigant during orthognathic surgery and concluded that there was a statistical significance in blood loss between the tranexamic acid irrigant and the saline control irrigant, with the tranexamic acid irrigant reducing mean blood loss by >25%

[161]. Gauze soaked in topical tranexamic acid is an effective way of gaining the hemostatic effects of tranexamic acid post-dental extraction patients. The use of a tranexamic acid mouthwash as a hemostatic agent in post-dental extraction patients is supported by Carter et al. who found favorable outcomes of a 4.8% tranexamic mouthwash four times a day for 7 days post-dental extraction compared to a fibrin glue preparation in patients on anticoagulant therapy [162, 163] (**Table 2**).

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