ORAL SURGERY

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Bleeding disorder

A number of procedures that are performed in dentistry may cause bleeding. Under normal circumstances, these procedures can be performed with little risk; however, patients whose ability to control bleeding is altered by congenital defects in coagulation factors, platelets, or blood vessels may be in grave danger unless the dentist identifies the problem before performing any dental procedure. In most cases, after a patient with a congenital bleeding problem has been identified, steps can be taken to greatly reduce the risks associated with dental procedures.

Hemophilia A:

The hemostatic abnormality in hemophilia A is caused by a deficiency or a defect of factor VIII. Factor VIII circulates in plasma bound to Von Willebrand factor (vWF). Unbound factor VIII is destroyed. Factor VIII was thought to be produced by endothelial cells and not by the liver, as most coagulation factors are. However, when disease was corrected by transplantation in several liver transplant recipients with hemophilia, it became clear that liver parenchymal cells also produce factor VIII.

Hemophilia A is inherited as an X-linked recessive trait. The defective gene is located on the X chromosome. An affected man will not transmit the disease to his sons; however, all of his daughters will be carriers of the trait because they inherit his X chromosome. A female carrier will transmit the disorder to half of her sons and the carrier state to half of her daughters. Severity of bleeding varies from kindred to kindred. Within a given kindred, the clinical severity of the disorder is constant; for example, relatives of people with severe hemophilia are likely to be affected severely. The mutation rate for the responsible gene is unusually high (up to 30%), which explains why a rare condition such as hemophilia A does not die out after several generations. Because of the high mutation rate of the responsible gene, a negative family history is of limited value in excluding the possibility of hemophilia A. The assay of factor VIII activity can be used to identify female carriers of the trait. About 35% of carriers will show a decrease in factor VIII (≈50% of normal factor VIII levels). Other carriers may have normal levels of factor VIII. Immunoassays for vWF can greatly improve the detection rate among carriers of hemophilia A. Polymorphic DNA probes are now available that are capable of detecting 90% of affected families and 96% or more of carriers. Hemophilia A can manifest in women. This occurs in a mating between an affected male and a female

carrier. Half of the daughters of such a mating would inherit two abnormal X chromosomes—one from the affected father and one from the carrier mother. These daughters would have homozygous hemophilia. In addition, hemophilia may occur in a minority of heterozygous carriers. Normal homeostasis requires at least 30% factor VIII activity. Symptomatic patients usually have factor VIII levels below 5%. Those with factor VIII levels between 5% and 30% have a mild form of the disease. Patients with levels between 1% and 5% have moderate disease, and severe forms of the disease occur when the level is less than 1% of normal. About 60% of cases of hemophilia are severe.

HEMOPHILIA B

In hemophilia B (Christmas disease), factor IX is deficient or defective. Hemophilia B is inherited as an X-linked recessive trait (F9 gene). Factor IX levels below 10% have been reported in a few women. Similar to hemophilia A, the disorder manifests primarily in males. Severe disease, in which affected patients have less than 1% of normal amounts of factor IX, is less common than in hemophilia A. Clinical manifestations of the two disorders are identical. Screening laboratory test results are similar for both diseases. Specific factor assays for factor IX establishes the diagnosis. Purified factor IX products are recommended for the treatment of minor and major bleeding. Recombinant factor IX is now available for clinical use.

Von Willebrand's disease

The most common inherited bleeding disorder is von Willebrand disease, which is caused by an inherited defect involving platelet adhesion. The cause of platelet dysfunction in von Willebrand disease is a deficiency or a qualitative defect in vWF.

The disease has several variants, depending on the severity of genetic expression. Most of the variants are transmitted as autosomal dominant traits (types 1 and 2). These variants of the disease tend to result in mild to moderate clinical bleeding problems. Type 1 is the most common form of von Willebrand disease. It accounts for about 70% to 80% of the cases. The greater the deficiency of vWF in type 1 disease, the more likely it is that signs and symptoms of hemophilia A will be found. Type 2 A is responsible for 15% to 20% of cases. The other variants of the disease are uncommon. Type 3, which is rare, is transmitted as an autosomal recessive trait that leads to severe deficiency of vWF and FVIII.

Variants of von Willebrand disease with a significant reduction in vWF or with a vWF that is unable to bind factor VIII may show signs and symptoms of hemophilia A, in addition to those associated with defective platelet adhesion.

in mild cases, bleeding occurs only after surgery or trauma. In the more severe cases—type 2N and type 3—spontaneous epistaxis or oral mucosal bleeding may be noted.

Thrombocytopenia:
It occurs when the platelet count that falls below the lower limit of normal, i.e., 150000/microliter (for adults). risks associated with thrombocytopenia range from no risk at all to bleeding risks and thrombosis. The correlation of severity of thrombocytopenia and bleeding risk is uncertain. Spontaneous bleeding can occur with a platelet count under 10000/microliter and surgical bleeding with counts below 50000/microL. Thrombocytopenia is associated with risk of thrombosis in conditions like heparin-induced thrombocytopenia (HIT), antiphospholipid antibody syndrome (APS), disseminated intravascular coagulation (DIC), thrombotic microangiopathy (TMA), paroxysmal nocturnal hemoglobinuria (PNH).

Infiltration and block injections of local anesthesia can be provided in patients with platelet counts above 30,000/μL. Also, most routine dental procedures can be performed. If the platelet count is below this level, routine dental treatment involving minor tissue injury should be delayed. For urgent or emergency dental needs, platelet replacement is indicated. If the platelet count is above 50,000/μL, extractions and dentoalveolar surgery can be performed. For more advanced surgery, the platelet count should be 80,000/μL and 100,000/μL or higher. Patients with platelet counts below these levels will need platelet replacement before undergoing the planned procedures.

Common causes of thrombocytopenia:

1- Primary immune thrombocytopenia (primary ITP). An autoimmune condition where antibodies are produced against platelets resulting in platelet destruction.

2- Drug-induced immune thrombocytopenia:

- Heparin-induced thrombocytopenia (HIT) - in this condition, anti-platelet antibodies activate platelets resulting in thrombosis (both arterial and venous)
- Quinine
- Sulfonamides, ampicillin, vancomycin, piperacillin
- Acetaminophen, ibuprofen, naproxen
- Cimetidine

3- Drug-induced non-immune thrombocytopenia. Drugs like valproic acid, daptomycin, linezolid cause thrombocytopenia by dose-dependent suppression of platelet production.

4- Infections:
    - Viral: HIV, hepatitis C, Ebstein-Barr virus, parvovirus, mumps, varicella, rubella, Zika viral infections can cause thrombocytopenia.
    - Sepsis causes bone marrow suppression.
    - Helicobacter pylori
    - Malaria
5- Hypersplenism due to chronic liver disease
6- Chronic alcohol abuse
7- Nutrient deficiencies (folate, vitamin B12, copper)
8- Autoimmune disorders like systemic lupus erythematosus, rheumatoid arthritis associated with secondary ITP
9- Pregnancy. Mild thrombocytopenia presents in gestational thrombocytopenia; moderate-severe thrombocytopenia can occur in preeclampsia and HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome
10- Aplastic anemia
11- Inherited thrombocytopenia. Often seen in children, rare in adults
    - Von Willebrand disease type 2
    - Alport syndrome
    - Fanconi syndrome.
    - Bernard–Soulier syndrome

Dental management of the patient with bleeding disorders

1- Patient Evaluation and Risk Assessment

• Evaluate and determine whether a bleeding disorder (e.g., hemophilia) exists.

• Obtain medical consultation if undiagnosed, poorly controlled, or if uncertain. Screen patients with bleeding history or clinical signs of a bleeding disorder with PT, PTT, TT, and platelet count.

2- Drugs

Analgesics Avoid aspirin, aspirin-containing compounds, and other NSAIDs; acetaminophen with or without codeine is suggested for most patients.

Antibiotics Not indicated unless acute infection is present.

Anesthesia Avoid block anesthetic injections in patients not on desmopressin, aminocaproic acid, or factor concentrates.

Allergy Patients placed on factor VIII replacement need to be observed for signs and symptoms of allergy.

3- Bleeding

These patients are at great risk of bleeding from invasive dental procedures. Special precautions must be taken before invasive procedures. Patients with mild to moderate hemophilia can be managed using desmopressin and aminocaproic acid for many dental procedures. Factor VIII replacement is needed for patients with more severe hemophilia. Patients who are low responders for inhibitors (antibody response to factor VIII) require higher doses of factor VIII. Patients who are high responders are most difficult to manage and require activated factor VII, porcine factor VIII, steroids, or other special preparations such as prothrombin complex concentrates or activated prothrombin complex concentrations.

4- Consultation

The patient's hematologist must be consulted before any invasive dental procedures are performed. The severity of disease must be established. The presence of inhibitors and level of response to factor VIII need to be determined. Determine if the patient can be managed with desmopressin and aminocaproic acid. Establish the type and dosage of factor replacement needed for invasive dental procedures or surgery. Determine if the patient can be managed in the dental office or will require hospitalization.

5- Devices

Splints: may be constructed before multiple extractions or surgical procedures in patients with severe hemophilia.

Drugs: Avoid all drugs that may cause bleeding, such as aspirin and other NSAIDs, certain herbal medications, and over-the-counter drugs containing aspirin.

6- Emergencies

Excessive bleeding may occur after invasive dental procedures or surgery. Systemic and local means may be required to control the bleeding. Allergic reactions may occur in patients receiving factor replacement.

7- Follow-up

Patients should be seen and examined for signs of allergy or bleeding within 24 to 48 hours after surgical procedures

Blood dyscrasias

Disorders of the RBCs

1- Anemia

Anemia is the reduction in the oxygen carrying capacity of the blood, it is associated with the decreased number of circulating RBCs or abnormalities in the Hemoglobin (Hb) contained in the RBCs, which is the oxygen carrying molecule of the erythrocytes, it is also responsible for the transport of CO2. Hb is a heterogeneous group of proteins consisting of 4 globin chains and 4 haem (heme) groups. In anemia Hb level is below 12 g/dl in adult female and below 13 g/dl in adult male. Anemia is not a disease but rather a feature or symptom that results from many underlying causes.

Types of anemia:

• Deficiency anemias: Iron deficiency anemia; it is caused by blood loss, poor iron intake, poor iron absorption or increased demands for iron. It is more common in women than in men due to blood loss during menstruation and pregnancy. Vitamin B12 (cobalamin) deficiency, Folate (Folic acid) deficiency and *Pernicious anemia*; (*Vit. B12 and folic acid are needed for RBCs formation and growth within the bone marrow. Vit B12 is bound to gastric intrinsic factor secreted by the parietal cells and absorbed in the terminal ileum, deficiency of the intrinsic factor causes Pernicious anemia*).

• Hemolytic anemias: Hemoglobinopathies; these are inherited abnormalities of the Hb formation like Sickle cell anemia and Thalassemia. Inherited abnormal function or structure of erythrocytes; Erythrocyte metabolic defects as in Glucose-6-Phosphate Dehydrogenase deficiency (G6PD). And Erythrocyte membrane defects as in Spherocytosis, Ovalocytosis and Stomatocytosis. Damage to erythrocytes; which could be autoimmune, drug induced or infective. Worldwide Malaria is the most common cause of hemolytic anemia.

• Other anemias: Aplastic anemia; it is a pancytopenia with a non-functioning bone marrow, many cases are idiopathic but possible causes include: Chemical like Benzene, drugs, hepatitis virus, irradiation and graft versus host disease.

Anemia caused by bone marrow infiltration by abnormal cells; like in Leukemia and Multiple Myloma.

Anemia associated with systemic diseases; like in chronic inflammation and connective tissue diseases such as Rheumatoid Arthritis, Liver disease, Hypothyroidism, Hypopituitarism, Hypoadrenocorticism, Uremia and HIV infections.

Oral manifestations

Pale mucosa, oral ulcerations, angular cheilitis, glossitis and loss of papillae with atrophic changes in the oral mucosa.

patients with iron deficiency anemia may develop Plummer-Vinson syndrome and burning mouth symptoms.

patients with hemolytic anemia, there may be oral evidence of jaundice due to excessive red cells destruction, the trabecular pattern of bone may be affected due to hyperplasia of marrow elements so radiographs show enlarged marrow spaces and osteoporosis, the trabeculae between the teeth appear horizontal (stepladder).

Skull radiographs show hair on end appearance due to the new bone formation on the outer table of the skull. Vaso-occlusive events can lead to osteomyelitis, necrosis and peripheral neuropathy. Dental hypoplasia and delayed eruption of teeth often occur.

Dental management

1- Identification of the conditions associated with anemia through obtaining careful history, the questions should include history of dietary intake, malnutrition, alcohol or drug use, history of blood loss especially for women during menstruation and pregnancy. The clinician should also identify signs and symptoms of anemia and can also order some screening tests, if the results of one of the tests or more are abnormal, the patient should be referred for medical evaluation and treatment.

2- the clinician should ensure that the patient's underlying condition is under therapeutic control before proceeding with routine dental care. Patients with signs and symptoms of anemia and Hb level below 11 g/dl with abnormal heart rate or reduced oxygen saturation (below 91% in oximetry) are considered unstable and routine dental treatment should be deferred.

3- Local anesthesia (LA) is satisfactory for pain control, conscious sedation can be given only if there is supplemental oxygen, elective operations under general anesthesia (GA) are not carried out when Hb level is below 10 g/dl.

4- In patients with G6PD deficiency, certain drugs should be avoided since they can cause hemolysis, such as Sulfonamides (Sulfamethoxazole), Aspirin, Chloramphenicol and to a lesser extent Penicillin, Strepromycin and Isoniazide. Also, dental infections should be avoided and if they occur, they should be treated effectively.
5- In patients with Sickle cell anemia, routine dental care can be provided for stable patients during non-crisis period, appointments should be short and the procedures should be not complicated, oral infections should be avoided, LA without vasoconstrictor for routine dental care is used while for surgical procedures LA with vasoconstrictor 1:100000 can be used. Barbiturates and strong narcotics should be avoided and Diazepam used when sedation is needed, prophylactic Antibiotics for surgical procedures are used, liberal use of Salicylates should be avoided and pain control can be achieved with acetaminophen (Paracetamol) and Codeine. In general infection, dehydration, hypoxia, acidosis and cold should be avoided in patients with Sickle cell anemia because the can precipitate acute crisis.

2- Polycythemia

It is an expansion mainly in the red cell population, it may be primary and idiopathic associated with normal erythropoietin level (Polycythemia Rubra Vera) PRV. It can also be secondary to tumors that release erythropoietin hormone. PRV is a disease of elderly and of smokers, it has a slight male predilection. Diagnosis of Polycythemia is made when Hb level is above 16.5 g/dl and hematocrit 48% in women and when Hb is above 18.5 g/dl and hematocrit 52% in men.

Dental management

• LA regional blocks should be avoided if possible.
• Conscious sedation can be given.
• GA is allowed.
• Susceptibility to thrombosis and hemorrhage should be considered.
• Cytotoxic chemotherapy may cause oral complications that require management.

WBCs Disorders

1- Leukemia

Is cancer of the WBCs that affects the bone marrow and circulating blood. It involves exponential proliferation of lymphoid or myloid cells. Leukemias is classified by the clinical course into: acute and chronic, and by the cell of origin into: lymphoid or myloid (non-lymphoid). In acute leukemia there is a rapidly progressive disease that result from accumulation of immature, functionless WBCs in the bone marrow and blood, it is more common than chronic leukemia. While in the chronic leukemia there is slower onset and the cells are more mature. There are 4 types of leukemia with many subtypes:

1. Acute Lymphoblastic Leukemia ALL, it is the most common type in children.
2. Acute Mylogenous Leukemia AML, the most common type in adults.
3. Chronic Lymphocytic Leukemia CLL, the second most common type in adults.
4. Chronic Myloid Leukemia CML.

Oral manifestations

Are more common in acute leukemia than in chronic leukemia, they include:

• Localized or generalized gingival enlargement, caused by infiltration of immature WBCs, it occurs in about 35% of acute leukemias and 10% of the chronic leukemias.
• The gingiva bleeds easily, sometimes spontaneously oral hygiene measures and chemotherapy may cause resolution.
• Oral ulcerations.
• Recurrent oral infections, due to the immature WBCs and as a complication of chemotherapy.
• Localized mass of leukemic cells in the gingiva and other site of the oral cavity, it is termed Chloroma (Granulocytic Sarcoma).
• Pallor of oral mucosa.
• LAP.

2- Lymphoma

Lymphoma is a solid malignant tumor that originate in the lymph nodes or extranodal lymphoid tissues in any part of the body. Lymphoma comprises Hodgkin's lymphoma or disease and non-Hodgkin's lymphoma NHL. NHL is more common than the Hodgkin's type.

1. Hodgkin's disease; it is a neoplasm of B lymphocytes; it contains a characteristic tumor cell (Reed Sternberg cell). The cause is unknown but EBV may be implicated. It presents as a painless enlargement of non-tender lymph nodes involving head and neck, axillary, mediastinal or groin lymph nodes. Fever, night sweats, fatigue and weight loss may be experienced by the patient. The diagnosis is based on nodal biopsy and bone marrow aspirate. Medical management requires staging on the basis of history, physical examination, lab. Findings and imaging.
2. Non-Hodgkin's lymphoma; a large group of lymphoproliferative disorders of either B lymphocytes (more than 80% of the cases) or T lymphocytes origin. There are many types of NHL. The cause is unknown but some genetic factors and chromosomal abnormalities in addition to other environmental factors such as infection with EBV, irradiation and drugs were implicated as possible causative factors. The clinical presentation includes; LAP, fever, weight loss, abdominal or chest pain and extranodal tumors. The diagnosis is based on biopsy of the lymph nodes or extranodal tumor. Proper staging is required which consists of blood investigation, imaging and bone marrow biopsy.

Oral manifestations

• Cervical LAP.

• Intraoral tumors that may involve Waldeyer's ring (named after the German anatomist Heinrich Wilhelm Gottfried von Waldeyer Hartz), salivary glands, mandible, palate, gingiva or floor of the mouth.

• Oral ulcerations.

• Oral complications secondary to treatment include; burning mouth symptoms, xerostomia, infections, trismus, impaired craniomandibular growth and osteoradionecrosis.

Burkitt's Lymphoma

It is an aggressive type of B cell NHL. It is the most common lymphoma of children. Types of Burkitt's lymphoma:

1. the endemic or African type.
2. non-endemic type, occurs in western societies.

3. recently described type associated with HIV infected individuals.

Oral manifestations

Include; tumors of the maxilla or mandible that cause bone destruction, mobility of the teeth, pain and paresthesia. On radiograph it appears as an osteolytic lesion with poorly demarcated margins.

Multiple Myeloma

It is a lymphoproliferative disorder that results from overproduction of cloned malignant plasma cells resulting in bony lesions involving the skeletal system.

Oral manifestations

• Painful bony lesions, that appear as osteolytic punched out lesions which may be associated with cortical bone expansion.
• Extramedullary plasma cell tumor.
• Deposition of Amyloid in soft tissues like tongue.
• Osteonecrosis of the bone associated with Bisphosphonates treatment; it usually appears after surgery especially tooth extraction as a painful, non-healing socket. Treatment is directed to limiting the progression of necrosis through debridement, irrigation with antiseptics and antibiotics.

Dental management of WBCs Dyscrasias

1- *History:* Identify and recognize the presence of WBCs disorders through history (signs and symptoms of these disorders, such as easy bruising or bleeding tendency) also family history of WBCs disorders.
2- *Examination:* Thorough extraoral and intraoral examination of the head and neck, oral cavity and oropharynx to identify any abnormalities that are suggestive of WBCs disorders. Screening blood investigations may be needed and if the results are abnormal, the patient is referred for further evaluation and routine dental care can be deferred.

Dental management of patients with diagnosed Leukemia, Lymphoma and Multiple Myeloma It involves the three phases of the medical therapy:

1- *Pretreatment assessment and preparation of the patient:* Full knowledge of the patient's condition is required, the aim of this phase is to prevent oral infections, all potential sources of infection must be eliminated through restorative, periodontal and surgical treatment preferably 3 weeks prior to medical treatment.

Oral hygiene measures should be encouraged. When extraction is planned it should be as conservative as possible avoiding any hemostatic packing agents and attaining primary closure.

Prophylactic antibiotic is recommended before oral surgical procedure, 2 g oral Penicillin 1 hour before the procedure, 500 mg 4 times daily for 1 week.

Patients with platelet count below 50.000/mm^3 should not undergo oral surgical procedures unless correction by transfusion is carried out.

2- *Oral health care during medical treatment:* during treatment the patient is susceptible to many oral complications that require care:

• Mucositis; appear 7-10 days after initiation of treatment and resolve after it. The non-keratinized mucosa is more severely affected. Oral hygiene measures should be maintained to minimize infection, antiseptic and antimicrobial mouth washes e.g. Chlorhexidin are recommended, topical anesthetics and systemic analgesics can be given.

• Neutropenia and Infection; neutropenia leads to gingival inflammation, oral ulceration and infection which can be severe but with minimal clinical signs. Unusual bacterial infections, fungal and viral infections occur in patients with Leukemia, Lymphoma and Multiple Myloma on chemotherapy and require treatment. When oral infections develop, a specimen of the exudate should be sent for culture and antibiotic sensitivity tests.

• Bleeding; thrombocytopenia may case submucosal hemorrhage and sometimes spontaneous gingival bleeding, oral hygiene measures should be improved, when bleeding occurs local hemostatic measures should be used first like using pressure, gelatin sponge with thrombin or the use of oral antifibrinolytic agents. If these measures fail transfusion may be needed.

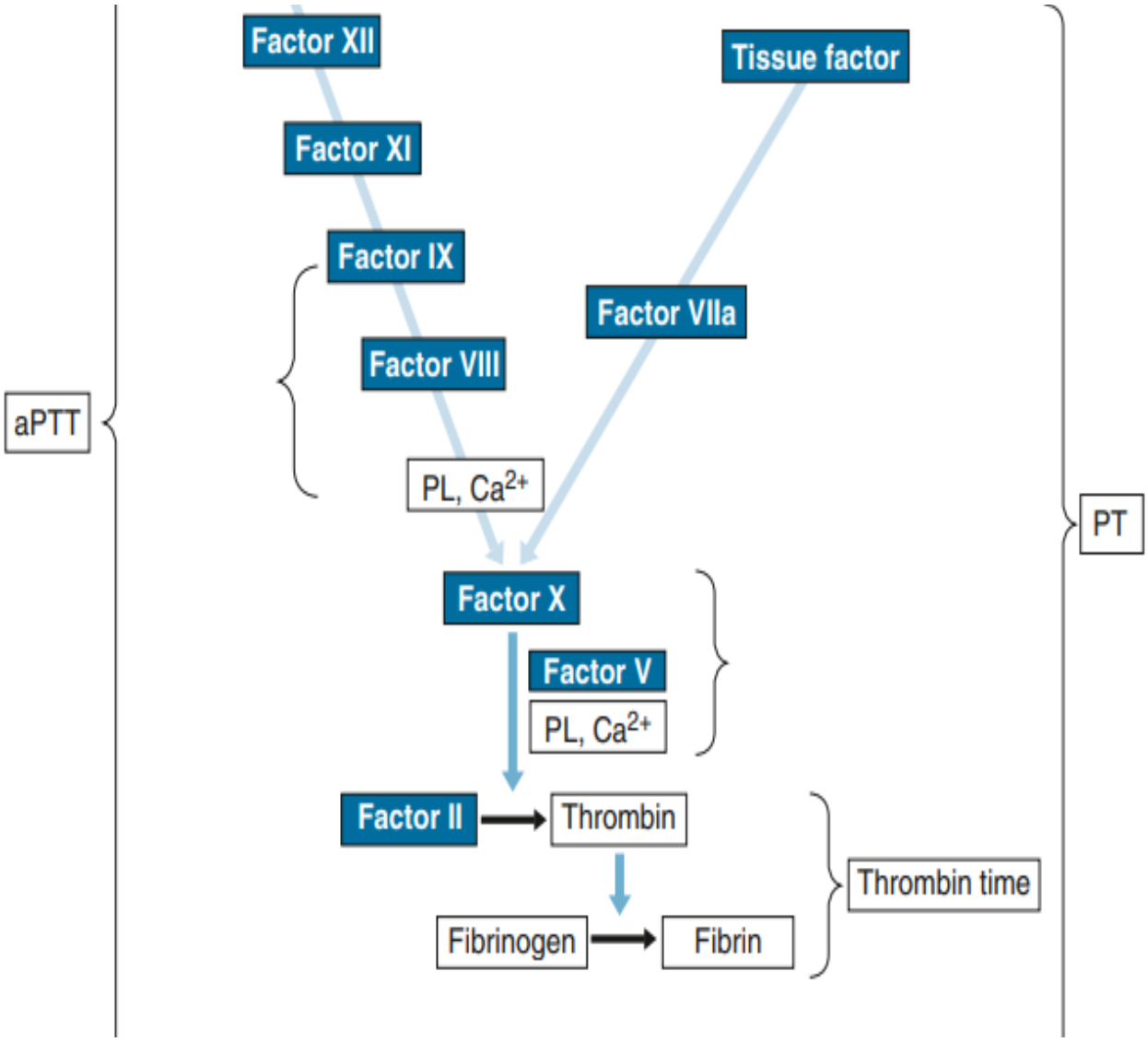
• Graft versus host disease; it occurs after bone marrow transplantation when immunologically active donor T cells react against host tissues, it can be acute (within 2-3 weeks) causing rash, mucosal ulcerations, increased liver enzymes and diarrhea. Or it could be chronic (3-12 months) producing features like Sjögren syndrome, scleroderma, lichenoid changes, xerostomia, mucositis, dysphagia and damage to liver. It can be prevented by corticosteroids and immunosuppressive drugs.

• Adverse effects of drugs; such as gingival overgrowth with patients taking Cyclosporine.
• Disturbance of growth and development; due to treatment with chemotherapy and radiotherapy during childhood leading to micrognathia, malocclusion and teeth abnormalities.

3- Posttreatment management: patients in remission state can have routine dental care while patients with poor prognosis should receive emergency care only. When invasive procedures are planned (e.g. oral surgery), platelet count and bleeding time should be investigated, the patient's physician should be consulted. In patients with surgically removed spleen, prophylactic antibiotic is needed, since they are at risk of bacterial infections, especially in the first 6 months after splenectomy. In patients with acute symptoms, routine dental care should be deferred. LA regional block should be avoided if possible, in patients with bleeding tendency. Conscious sedation can be given and GA is allowed.

BOX 24.2 Normal Control of Bleeding

1. Vascular phase:
   a. Vasoconstriction occurs in area of injury, and increase in extravascular pressure.
   b. Begins immediately after injury.
2. Platelet phase:
   a. Platelets and vessel wall become "sticky" and adhere.
   b. Activation and aggregation of platelets results in formation of a mechanical plug and scaffold for coagulation.
   c. Begins seconds after injury.
3. Coagulation phase:
   a. The initiation of coagulation occurs at the site of injury via the tissue factor pathway (extrinsic pathway).
   b. Propagation of coagulation via the tissue factor pathway then activates the intrinsic pathway which more strongly activates factor X to form thrombin.
   c. Final coagulation to produce the fibrin clots occurs through the common pathway.
   d. Takes place more slowly than other phases.
4. Fibrinolytic phase:
   a. Release of plasminogen which is converted to plasmin on the clot.
   b. Plasmin cleaves and dissolves the fibrin into fibrin degradation products.


Factor XII
Tissue factor
Factor XI
Factor IX
Factor VIIa
Factor VIII
aPTT
PL, Ca2+
PT
Factor X
Factor V
PL, Ca2+
Factor II
Thrombin
Thrombin time
Fibrinogen
Fibrin

BOX 24.6 Screening Laboratory Tests for Detection of a Potential "Bleeder"

1. PT—activated by tissue thromboplastin:
   a. Tests extrinsic and common pathways.
   b. Control should be run.
   c. Normal PT is 11—15 s, depending on laboratory.
   d. Control must be in normal range.
2. aPTT—initiated by phospholipid platelet substitute and activated by addition of contact activator (kaolin):
   a. Tests intrinsic and common pathways.
   b. Control should be run.
   c. Normal aPTT is 25—35 s, depending on laboratory.
   d. Control must be in normal range.
3. TT—activated by thrombin:
   a. Tests ability to form initial clot from fibrinogen.
   b. Controls should be run.
   c. Normal TT is 9—13 s.
4. Platelet count:
   a. Tests platelet phase for adequate number of platelets.
   b. Normal count is 140,000—400,000/μL.
   c. Clinical bleeding problem can occur if count is less than 50,000/μL.

aPTT, activated partial thromboplastin time; *PT*, prothrombin time; *TT*, thrombin time.