The anemias

Anemia is a disease of oxygen transport. Tissues supplied by the circulation receive a deficient quantity of oxygen. This deficient oxygenation can be attributed to a decrease in erythrocyte numbers, decreased amounts of hemoglobin, or defective hemoglobin molecules. Therefore, there are numerous forms of anemia that differ depending upon where the defect lies. The most common form of anemia is attributed to iron deficiency and is, therefore, easily treated by increasing intake of dietary iron or iron-salt tablets. The other forms of anemia are less frequently encountered, particularly those that are heritable and involve defective hemoglobins, which predispose erythrocytes to lysis (hemolytic anemias). In general, anemias do not pose a serious risk for patients seeking dental care, unless general anesthetics are to be administered. Some forms of anemia are associated with oral mucosa lesions and radiographically evident changes in the jawbones.

Molecular and pathologic correlates of disease

Erythroblasts are generated in the bone marrow from hematopoietic stem cells. Their differentiation into mature erythrocytes requires the action of erythropoietin, a growth factor that is secreted into the bloodstream by renal tubular epithelium. Other hematopoietic growth factors secreted by connective tissue cells also play a role in red blood cell maturation. Erythrocytes are basically anuclear bags of hemoglobin, the molecule responsible for oxygen transport. Hemoglobin is synthesized in nucleated erythroblasts and requires folic acid and cyanocobalamin (vitamin B12) for full maturation. The molecule is comprised of a heme (porphyrin) ring with ferric ions chelated in the center of the ring; globular protein components are attached to the heme ring to complete the structure of this complex protein. These globin chains are subdivided into alpha and beta subunits. In utero, a special type of hemoglobin is synthesized (fetal Hgb [Hgb F]). After parturition, chemically...
distinct adult hemoglobin is produced (Hgb A), and subsequently, the cell loses its nucleus. The average life span of an erythrocyte is 120 days, after which it is lysed and phagocytized by macrophages in the liver. The heme ring is transformed to bilirubin and metabolized through the liver, the globin chains are degraded reconstituting the amino acid pool, and the iron is recycled back into newly generated erythrocytes.

Anemia attributable to iron deficiency and blood loss is characterized by a decrease in circulating erythrocytes (Figure 8–1). The cells are small and hemoglobin-deficient (microcytic, hypochromic anemia). Megaloblastic anemias, because of the erythroblasts, faced with a deficiency in the factors that are required for hemoglobin synthesis, tend to enlarge and pack as much hemoglobin into the cell as possible. There is a decrease in erythrocyte numbers, whereas the individual cells are large and contain concentrated hemoglobin (macrocytic, hyperchromic anemia). By comparing the red cell count, hemoglobin concentration per 100 mL of blood, and the packed cell volume, also termed the hematocrit, one can determine cell size and hemoglobin content. Ratios are obtained and are referred to as the red cell indices. Mean corpuscular volume (MCV) is derived by a calculation that compares the red cell numbers with the hematocrit. If cell number is normal (ie, $5 \times 10^6$) yet the hematocrit is low (far less than 45%), the MCV will be a lower value, indicating that the cells are microcytic. Conversely, if the red cell count is low (eg, $3 \times 10^6$) yet the hematocrit is normal (45%), the cells are macrocytic. The mean corpuscular hemoglobin concentration (MCHC), is a measure of the amount of hemoglobin within the cell. This ratio is derived by calculating the hemoglobin concentration in reference to the cell size. A low MCHC is seen in hypochromic anemias, whereas a high MCHC is indicative of hyperchromic anemia.

The hemolytic anemias are inherited defects of hemoglobin or red cell structure, sickle cell and thalassemia being the more common forms. In sickle cell anemia, one amino acid is substituted as a single base-point mutation, such that valine is substituted for glutamic acid at the sixth position of the beta chain. The protein conformation is changed by this mutation, and the cells assume a sickled shape and become lysed. Hemoglobin electrophoresis reveals the presence of both Hgb A and Hgb S in heterozygotic carriers, with only Hgb S being detected in homozygous subjects with full-blown sickle cell anemia. There are numerous variants of thalassemia, all of which involve mutations in specific loci of either the alpha or beta globin chains. As in sickle cell, the Mediterranean anemias result in altered erythrocyte morphology and predispose to lysis. There is considerable variability with regard to severity of disease in the different subtypes of thalassemia. Hereditary spherocytosis is a disease of red cell morphology and is probably attributable to a derangement in the erythrocyte cytoskeletal molecule spectrin. The consequence is a change in shape of the erythrocyte, whereby it loses its discoid structure and becomes spherical. The spherocytes are readily lysed in the spleen. In glucose-6-phosphate dehydrogenase deficiency, the red cell is easily damaged and becomes lysed. This occurs because enzyme dysfunction leads to low levels of reduced glutathione, a molecule that when present in normal concentration, protects erythrocytes from oxidants.

In Fanconi anemia, there is a mutation in the DNA repair gene family, a defect that leads not only to ane-

![Normocytic normochromic](image1)

![Microcytic hypochromic](image2)

![Macrocytic hyperchromic](image3)

**Figure 8–1** Top, Red cell sizes and hemoglobin content in various anemias. Bottom, Normal hemogram. MCV = mean corpuscular volume; MCHC = mean corpuscular hemoglobin concentration; RBC = red blood cell count.

<table>
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<td>Maturation defects and deficiency anemias</td>
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<td>Internal hemorrhage</td>
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<td>Glucose-6-phosphate dehydrogenase deficiency</td>
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<td>Hereditary spherocytosis</td>
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mia but to a predisposition for squamous cancers, many of which affect the facial skin and oral mucosa.

Clinical features

Table 8–1 lists the more common forms of anemia. Iron deficiency is most common and is characterized by palor and lethargy. The hemogram shows low red cell count, hemoglobin, and hematocrit, with hypochromatic microcytic erythrocytes. Females are affected far more frequently than males. The anemia can be reversed by adding adequate levels of iron to the diet. Iron deficiency among women of Scandinavian descent that is associated with atrophic changes in the upper aerodigestive tract mucosa is termed the Plummer-Vinson syndrome, and the atrophic mucosa is prone to malignant transformation to squamous cell carcinomas.

Internal hemorrhaging occurs in a variety of clinical situations, including visceral trauma, esophageal varices accompanying alcoholic cirrhosis, bleeding gastric and pyloric ulcers, and bleeds into the gut from ulcerated colonic cancer. Another systemic disease associated with anemia is end-stage kidney disease. Recall that erythropoietin is synthesized by the kidney tubule, and in tubulointerstitial renal diseases as well as late-stage glomerulonephritis and pyelonephritis, tubular epithelial necrosis occurs with a resultant decrease in erythropoietin levels.

Dietary folic acid deficiency and vitamin B₁₂ deficiency secondary to atrophic gastritis and loss of intrinsic factor lead to megaloblastic anemia, with decreased red cell numbers showing macrocytic hyperchromic changes. In fact, one may produce adequate numbers of these cells and still be anemic because the overall oxygen-carrying capacity is diminished. Anemias that occur as a result of dietary or absorption deficiency of folate or vitamin B₁₂ are referred to as megaloblastic anemias. Patients are constantly run down and tired, with skin palor. Folic acid deficiency can be corrected by dietary supplementation. Vitamin B₁₂ deficiency requires injection administration of vitamin B₁₂, because the atrophic gastric mucosa that is an accompaniment is unable to synthesize adequate levels of intrinsic factor, a protein involved in B₁₂ absorption and transport.

Aplastic anemia is a hematologic disease that affects not only erythrocytes but white cells and platelets as well. There is widespread bone marrow arrest in aplastic anemia that is clinically characterized by palor, susceptibility to infections and hemorrhagic diathesis. Bone marrow aplasia is also seen in Fanconi anemia. Patients with Fanconi manifest congenital anomalies, including digital defects of the thumb and radii, and develop facial skin or oral squamous cell carcinomas at a young age.

The hemolytic anemias are encountered in children, since they represent mutations in the hemoglobin mole-
lost, leaving a smooth, reddened dorsal surface (Figure 8–3). Patients presenting with tongue changes of this nature may also have erythematous candidiasis, but a hematologic workup is required to uncover anemia. Folate and B12 serum levels should be ordered along with a hemogram, to disclose macrocytic hyperchromic anemia. Iron deficiency anemia can also be manifested by a depapillated tongue that may also be associated with discomfort.

In sickle cell anemia, stepladder trabeculation may be seen on dental bitewing radiographs, a finding that is common yet may be seen in patients without sickle cell disease. Increased hematopoiesis leads to radiographically defined changes in the calvarium whereby vertical projections of osteophytes are seen, yielding a “hair on end” effect. Similar changes may be encountered in thalassemia syndromes, and additionally, the jaws may exhibit multilocular radiolucencies (Figure 8–4).

Dental management

In general, there are no increased risks that require treatment precautions for anemic patients undergoing dental procedures. If the anemia is severe, patients have a tendency for syncope and should be closely monitored. In aplastic anemia, it must be recalled that a potential bleeding disorder is inherent and, therefore, a platelet count should be ordered prior to undertaking any surgical procedures. Sepsis is also of concern in aplastic patients with significant neutropenia. If the neutrophil count is less than 2500/mm³ and dental, periapical, or periodontal acute infection is evident, antibiotic coverage is recommended after any periodontal, endodontic, or oral surgical procedures. For patients being placed under inhalation anesthesia for dental procedures, oxygenation is crucial. The anesthetist should address these issues.

Children with sickle cell anemia should be assessed dentally on a regular basis to ensure that dental and periodontal infections are eliminated, since a severe dental infection may precipitate a crisis attack. If nitrous oxide analgesia is to be administered, high oxygen levels must be maintained with a high flow rate.

Leukemias and lymphomas

Leukemias and lymphomas account for approximately 8% of all malignancies and presently represent almost 95,000 new cases diagnosed each year in the United States. In 2000, it was estimated that 62,300 were lymphomas (54,000 non-Hodgkin type) and 30,800 were leukemias. These malignancies afflict slightly more males than females. More than half of those afflicted will die from their disease. In children ages 1 to 14 years, malignancies are the leading disease-cause of death; leukemia is the most common malignancy within this cohort. Acute myelogenous leukemia (AML) occurs in all decades of life, but is primarily found in patients over the age of 40 years. Chronic myelogenous leukemia (CML) generally occurs in individuals older than 20 years, with frequency increasing with each succeeding decade. Lymphomas collectively represent several types of neoplasias of the lymphoreticular system.
that share clinical characteristics. Distribution in humans varies. For example, incidence of Hodgkin disease exhibits two peaks: early adulthood and beyond the fifth decade. Multiple myeloma, which is diagnosed in almost 14,000 Americans each year, primarily affects patients older than 40 years.

Leukemia and lymphoma collectively represent a varied pattern of white blood cell abnormalities, a wide spectrum of signs and symptoms, and a spectrum of management approaches. A wide range of oral lesions can arise in patients with these diseases (Table 8–2). Presenting symptoms and signs as well as cancer treatment strategies are relevant to the dental practitioner regarding diagnosis and dental treatment. In many instances, oral lesions may be the first indication of the underlying leukemia or lymphoma. Furthermore, these patients can develop a high risk for systemic infection of oral origin secondary to their underlying disease or cancer therapies, which produce profound, prolonged immunosuppression.

**Molecular and pathologic correlates of disease**

Leukemias are neoplasms of the white blood cells. The disease occurs in all races and may develop at any age. In the United States, approximately 30,800 new cases of leukemia occurred in 2000. Approximately 50% of leukemia cases observed in Western countries are acute leukemias, about 30% being chronic lymphocytic leukemia (CLL) and about 20% being CML. Leukemias exhibit a slight predilection for males.

Leukemia can be caused by exposure to chemical carcinogens or high-dose ionizing radiation. Chemicals and drugs associated with development of leukemia include benzene, phenylbutazone, arsenic, and chloramphenicol. Genetic susceptibility also appears to increase risk of disease. Although animal models have established a role for oncogenic viruses in causing the disease, viral causation of human leukemia is not fully substantiated. Human T-lymphotrophic virus (HTLV-1) is linked to human adult T-cell leukemia/lymphoma. Despite widespread distribution of this virus worldwide, it accounts for a remarkably low percentage of leukemia in humans. Fulminant infection and hemorrhage are primary causes of death.

The classification of leukemia as acute or chronic principally depends on degree of white cell maturation (Figure 8–5) as well as cell-type of origin (eg, lymphocyte, granulocyte). Immunohistochemistry further aids in classifications that have direct implications for disease course, type, response to therapy, and long-term patient survival.

Clonal expansion of tumor cells can compromise normal hematopoiesis. This impairment results from the relentless mitosis of the leukemic cells, with resultant physical crowding of marrow spaces. In addition, leukemic cells appear to exert a chemically mediated inhibitory effect on normal hematopoiesis. Over time and as tumor burden increases, a functional neutropenia as well as thrombocytopenia and anemia may emerge. Increasing presence of leukemic blast cells in the peripheral blood occurs as disease progresses. Blast cells are incapable of normal physiologic and protective functions. Gene deletions and translocations on various chromosomes have been identified. These findings add
to a better understanding of these malignancies regarding causation, patient risks, therapy, and prognosis.

Lymphomas represent malignant disorders of lymphocytes, histiocytes, and their precursors or progeny. The term malignant lymphomas refers to several neoplastic diseases of the lymphoreticular system that include Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, multiple myeloma, and mycosis fungoides.

An important distinction exists between Hodgkin lymphoma and non-Hodgkin lymphoma. Hodgkin lymphoma is characterized by morphologically distinct neoplastic giant cells (Reed-Sternberg cells), distinctive clinical features, including fever, and an uncertain target cell associated with the neoplastic transformation (Figure 8–6). The disease displays a bimodal age-and-incidence curve; one peak is associated with early adult life (under 30 yr of age), and the second peak with patients older than 45 years. There is no racial predisposition.

By comparison, non-Hodgkin lymphoma represents a wide range of disorders with associated important variations in patient age at onset, primary cell of origin, and therapeutic response. The diseases collectively range from relatively indolent to rapidly fatal malignancies. Etiology of these lymphomas remains unknown, although radiation, viral infections, and immune deficiencies have been implicated. Approximately 55,400 new cases of non-Hodgkin lymphoma were diagnosed in the United States in 2000; a significant proportion occurs in immunosuppressed patients. The 30 to 40% 5-year survival rate associated with the disease is less favorable than that for Hodgkin disease. Non-Hodgkin lymphoma is the most rapidly escalating neoplasm in terms of frequency in human immunodeficiency virus (HIV)-infected patients, and is virtually fatal in this cohort (see Chapter 14).

Less common lymphomas include Burkitt lymphoma, mycosis fungoides, and lymphomas secondary to midline “nonhealing” granuloma. Collectively, these conditions affect all ages of patients. The African form of Burkitt lymphoma has a distinct association with Epstein-Barr virus, whereas the American form shows little association with the virus. The African form

Figure 8–5 Maturation and differentiation of blood leukocytes in reference to leukemias and lymphomas.
exhibits a predilection for the mandible, whereas the American version typically initially involves lymph nodes and bone marrow. The neoplasms are treated with chemotherapy or radiation. They are not discussed further in this chapter because of their relatively low frequency of occurrence worldwide.

The non-Hodgkin lymphomas are subdivided into numerous variants, based on cellular phenotype, cell size, and formation or lack of formation of follicular structures (Figure 8–7). A combined American and European histopathologic classification system is used to standardize the morphologic diagnosis, which in turn is related to prognosis and response to radiation and specific chemotherapeutic agents. The lymphoid cells may be of B or T origin; immunohistochemical or flow cytometric analysis can be used to phenotype the tumor. All tumor cells in the mass are monoclonal, being derived from a single stem cell that has undergone neoplastic transformation. Clonality can be assessed by gene rearrangement studies that sample fresh tissue and determine if the B-cell immunoglobulin receptor or, in the case of T-cell lymphomas, the T-cell receptor is chemically identical for all tumor cells, thereby confirming monoclonality. As with leukemias, lymphoma cells harbor specific translocations of chromosomes and express increased levels of specific oncogenes and transcription factors, cell cycle regulatory molecules, and mutated tumor-suppressor genes.

Clinical features, diagnosis, and treatment

Leukemia
Acute leukemia can affect any component of the myeloid series (Figure 8–8); classically, the disease can be categorized into acute lymphocytic or acute myelogenous leukemia. The disease is typically aggressive and can lead to death within 6 months unless intensive cancer therapy is promptly initiated. Signs and symptoms of acute leukemia are associated with progressive marrow involvement secondary to expanding tumor burden and loss of normal hematopoietic cells. Patients with leukemia typically complain of fatigue, malaise, and occasional fever; they may also be aware of neck swelling or unexplained gingival bleeding. This constellation of symptoms may prompt them to seek dental evaluation. Infection, lymphadenopathy, night sweats, and weight loss may also be present.

The resulting neutropenia, anemia, and thrombocytopenia can lead to viral, bacterial, or fungal infection as well as fatigue, dypsnea on exertion, pallor, palpititations, and spontaneous hemorrhage. In addition, leukemic infiltrates can involve organ systems, including the oral cavity, especially gingiva. The diagnosis is suspected by history and clinical findings and is confirmed and staged by hematology and bone marrow assessment.
CHAPTER 8

Treatment of acute lymphocytic leukemia can be divided into three phases. First, high-dose chemotherapy (remission induction) is administered, with a goal of eradicating microscopically detectable disease. Second, central nervous system (CNS) prophylaxis is instituted via intrathecal chemotherapy or carinal radiation, to eliminate tumor burden in the CNS. Third, maintenance chemotherapy is administered over the several years following completion of high-dose chemotherapy, to maximize length of disease-free status. This collective approach is associated with 50 to 80% of patients achieving a 3-year disease-free survival, with 75% of these patients cured of disease and requiring no further chemotherapy. In relapsed patients, allogeneic hematopoietic cell transplantation of bone marrow or peripheral blood origin is associated with approximately 50% long-term remission.

Acute myelogenous leukemia is considerably less sensitive to chemotherapy than is acute lymphocytic leukemia. Thus, AML is typically treated with more intensive therapy, including high-dose chemotherapy (induction phase) followed by moderately intense chemotherapy (maintenance phase). Induction therapy can produce short-term remission in 50 to 70% of patients, but long-term survival is generally only 1 to 2 years. Relapsed disease tends to exhibit increased resistance to subsequent high-dose chemotherapy. However, use of hematopoietic stem cell transplantation in recent years has improved long-term survivor data from less than 20% without transplant to 40 to 50% long-term remission with transplant.

Chronic leukemia can present insidiously, with diagnosis occasionally established during medical evaluations for other purposes. The disease typically progresses in indolent fashion; survival times in general are considerably longer with chronic leukemia than with acute leukemia. Chronic myelogenous leukemia is characterized by a profound leukocytosis characterized by multiple stages: (1) an initial chronic phase, in which an indolent elevation of white blood cells persists for several years; (2) an accelerated phase, in which white blood cell counts continue to increase despite the use of previously effective chemotherapy; and (3) ultimately, blast crisis, in which the disease clinically progresses in ways similar to acute leukemia, including resistance to chemotherapy. Currently, CML is principally managed via combined high-dose chemotherapy. However, expected life span is less than 1 year when the patient enters the blast crisis phase. Supralethal chemotherapy followed by stem cell transplant is emerging as an efficacious modality, with complete remissions being currently achieved in 40 to 50% of patients.

In contrast, CLL generally occurs in older adults; patients less than 35 years of age are rarely affected. The disease in the older age group is only slowly progressive, with patient survival often consistent with otherwise healthy peers. However, younger patients experience a more rapid disease progression, with expected life span of approximately 5 to 7 years.

Lymphomas

**Hodgkin lymphoma**

Initial clinical disease expression is generally associated with regional lymph nodes above the diaphragm. Head and neck nodes are involved in 60 to 80% of presenting cases. Clinical progression over time is varied and related to stage of disease at diagnosis. Diagnosis and staging involve microscopic lymph node confirmation and assessment of the extent of lymph node involvement. Localized cervical disease conveys an optimal prognosis and is generally responsive to localized radiation. However, in advanced cases, combinations of radiation and chemotherapy are used. The clinical course is typically one of cycles of remission followed by acute flares of the disease. Hematopoietic cell transplantation is being used with increasing frequency and success.

**Non-Hodgkin lymphoma**

The most prominent presenting feature in non-Hodgkin lymphoma is painless firm lymphadenopathy, with a predisposition to supraclavicular or cervical regions. Tumor masses can be extranodal (Figure 8–9). Patients also typically present with findings that include fever, unexplained weight loss, fatigue, diaphoresis, and pruritus. The diagnosis and staging, in addition to history and physical examination, involve microscopic confirmation (lymph node or extranodal
biopsy), hematologic and bone marrow evaluations, and magnetic resonance imaging (MRI). Treatment involves combinations of high-dose chemotherapy and radiation.

Multiple myeloma
Multiple myeloma represents a neoplasm of plasma cells in which tumor expansion produces a monoclonal gammopathy. Significant marrow compromise develops over time, with attendant leukopenia, anemia, and bleeding diatheses. In addition, multifocal lesions of bone, including the mandible and maxilla, can lead to pathologic fractures and pain. Prognosis is poor, with survivorship usually being less than 2 years following diagnosis.

Oral manifestations and their treatment

Head and neck symptoms and signs, including painless cervical lymphadenopathy or spontaneous gingival hemorrhage, can cause the patient to present for assessment by the dentist. Painless extraoral swelling, acute oral infections, and gingival enlargement or bleeding that cannot be exclusively attributed to local factors should prompt the dentist to consider systemic disease that includes these neoplasms.

Lymphadenopathy
Many of the lymphomas display cervical lymphadenopathy early in the clinical course. Approximately 23% of non-Hodgkin lymphomas occur within Waldeyer ring in the nasopharynx. Characteristics include firm, immobile painless masses with ill-defined borders. Unilateral distribution is a classic hallmark, although bilateral distribution does not rule out neoplasia. Biopsy is required to produce a definitive diagnosis.

Acute oral infections
Infections can be classified in two domains: lesions occurring in the undiagnosed patient and those occurring secondary to cancer therapy.

Infections occurring in the undiagnosed patient
The patient may present with mucosal, periodontal, or periapical infections that are disproportionately severe in relation to local etiologic factors. In addition, diagnosis of oral lesions not responding appropriately to routine therapy should be reconsidered, including a possible systemic basis. These infections should be evaluated in the context of a thorough health history with specific attention to systemic symptoms described previously in this chapter. Although oral infection management, including culturing, antibiotics, and surgical intervention where indicated, is important, referral to a

Figure 8–9 Non-Hodgkin lymphoma (NHL): A, gingival NHL in an HIV-positive patient who was severely immunocompromised; B, palatal NHL manifested as a slow-growing mass.

Figure 8–10 Panoramic radiograph delineating periapical pathosis associated with the mandibular left first molar. The patient was newly diagnosed with acute leukemia in blast crisis and had developed left mandibular space infection secondary to functional neutropenia and periapical disease. Despite aggressive oral and systemic therapy, the patient expired several days after presenting with the condition.
physician for additional evaluation of possible systemic cause is warranted.

Upon confirmation that leukemia or lymphoma has been diagnosed, the dental team plays a pivotal role in preparing the patient for cancer treatment, which both directly and indirectly involves oral tissues. Supportive care, including infection prevention, remains a hallmark of treatment of oral lesions prior to cancer therapy. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, owing to deleterious effects on platelet adhesiveness. Invasive procedures, including periodontal scaling or dental extractions, should be performed in the context of consultation with the oncologist. Hematologic status and need for antibiotic prophylaxis if an in-dwelling catheter is present must be considered.

Infections occurring secondary to cancer therapy

The oral cavity represents a frequent portal of entry for systemic infection. Risk of infection escalates as the degree and duration of myelosuppression increases. In the patient with severe myeloablation, infections, including those of oral origin, can be fatal. Infections can develop at oral sites exhibiting chronic infection pre-chemotherapy (eg, chronic periodontal disease) or can occur in the context of nosocomial organisms. Bacterial infections. Oral bacterial infections observed in myelosuppressed cancer patients are often those associated with periodontal and endodontic disease, although mucosal infection can emerge as well (Figures 8–10 and 8–11). Organisms typically classified as being of low virulence in immunocompetent patients can produce both local and systemic infection in these patients. Examples include gram-positive organisms including viridans streptococci and Streptococcus mutans. Furthermore, pathogens, including Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli can emerge and cause infection of oral origin. These latter organisms are highly pathogenic and can result in death or substantial morbidity. Infection management should target these organisms in preventive or therapeutic regimens. Microbiologic documentation of causative organisms is essential in view of the nonspecific presentation of bacterial infections. It is important to recognize that secondary bacterial infection can occur with a wide range of oral lesions that may develop during myelosuppression.

Although not frequent in cancer patients with neutropenia cancer, acute exacerbation of preexistent periodontal disease can develop, with resultant systemic sequelae, including bacteremia. Clinical presentation can be subtle, since erythema and other inflammatory signs are typically suppressed during periods of profound myeloablation. Dental plaque can substantially increase risk of periodontal and associated systemic infection. Broad-spectrum antibiotic therapy should be considered while culture results are pending. In addition to systemic antimicrobials, oral interventions can include irrigation with effervescent (peroxide) agents, which are toxic to anaerobic bacteria colonizing the periodontal pocket, as well as gentle mechanical plaque removal, including dental brushing and flossing. Fungal infections. Candidal infections are the most frequent oral fungal infections in the myelosuppressed or xerostomic cancer patient (Figure 8–12). The combination of myelosuppression, xerostomia, antibiotic-mediated floral shifts, and mucosal disruption and immune dysregulation contributes to clinical disease. The pseudomembranous variant occurs most often, although erythematous, hyperplastic, or invasive infection may also emerge. During periods of profound immunosuppression, invasive fungal infections caused
by organisms including aspergillus, histoplasmosis and mucormycosis may develop.

Relative to establishing a diagnosis, culturing is indicated for clinically-suspected pseudomembranous candidiasis. However, culturing may produce false-negative results involving other types of fungal infection. Gram stain or potassium hydroxide stain of scrapings is often helpful in identifying the presence of fungus. Biopsy may also be useful; but interventions including antibiotics or platelet support may be indicated depending on the hematologic status of the patient.

Treatment requires the use of antifungal drugs (see Chapter 18). Systemic fluconazole prophylaxis is often effective in preventing fungal infections during myeloblation. Topical medications include clotrimazole troches, nystatin oral suspension, pastilles, and amphotericin oral suspension. Compliance with drug dosing coupled with optimal oral hygiene should be reinforced. Hydrogen peroxide-saline mouthrinses (equal parts 3% hydrogen peroxide and normal saline) and 0.12% chlorhexidine can be effective against mild cases, although the products can be irritating when mucositis is present. Ultimate resolution of infection may not occur until marrow recovery is well established.

Viral infections. Viral infections represent important and frequent clinical complications in the myelosuppressed cancer patient (Figure 8–13). Many, but not all of the infections represent reactivation of latent virus, including herpes simplex virus (HSV), varicella zoster virus (VZV), or cytomegalovirus (CMV). Resulting ulcerations can be painful and persistent. Oral lesions caused by CMV, VZV, adenovirus, and coxsackie virus are occasionally observed in these patients, although HSV represents the most common viral infection with oral manifestations. Diagnosis is established best by culture techniques.

Treatment requires the use of antiviral drugs (see Chapter 13). Oral or parenteral acyclovir is the drug of choice for HSV prophylaxis and therapy. The drug is highly effective in both settings, with viral resistance being a rare occurrence. Patients who are seropositive prior to myeloablation should receive prophylactic drug during the period of marrow suppression. Oral dosing is often appropriate unless the patient has oral mucositis sufficiently severe to preclude enteral administration. Valacyclovir recently has been shown to provide enhanced plasma levels. Acyclovir or famciclovir are used for VZV infections; CMV is treated with ganciclovir.

Gingival enlargement or bleeding
Gingival infiltrates are classically associated with myelogenous leukemia but can occasionally occur with lymphocytic leukemia or lymphoma (Figure 8–14). Infiltrates are characterized by edematous, engorged, and painful periodontium that can bleed easily. The gingival changes are disproportionately severe in relation to local etiologic factors. Maintenance of optimal oral hygiene is essential to minimizing complications. Supportive care, including topical and systemic antibiotics or hemostatic measures may

Figure 8–13  A, Severe herpes virus infection of mandibular labial mucosa in a myelosuppressed hematopoietic cell transplant patient. This lesion has several clinical features consistent with chemotherapy-induced oral mucositis. Differential diagnosis should thus include both herpes virus and chemotherapy-associated mucositis during the first 3 weeks post-transplantation. B, Reactivation of the varicella virus causing herpes zoster (shingles) in an immunosuppressed patient undergoing chemotherapy.

Figure 8–14 Gingival leukemic infiltrate in a patient newly diagnosed with acute myelogenous leukemia.
be necessary prior to performing dental scaling and prophylaxis. However, primary management consists of induction/remission chemotherapy, whereby tumor burden can be substantially reduced or eliminated. Low-dose (e.g., 900 cGy) radiation may be indicated in instances of gingival lesions that persist following chemotherapy.

Management of the oral cavity during myelosuppression

As previously noted, the myelosuppressed cancer patient is at high risk for acute local and systemic infection of oral origin. In addition, high-dose chemotherapy with or without stem cell rescue, or high-dose

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<td>Stage I. Pretransplant patient assessment and identification of donor (prior to day –10) Comprehensive medical evaluation Decision on donor (autologous, allogeneic, matched or unmatched)</td>
<td>Nausea and vomiting Fevers of unknown origin Veno-occlusive disease Acute GVHD</td>
<td>Elimination of oral foci of infection and trauma</td>
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<td>Stage II. Conditioning to early engraftment (days –10 to +21) High-dose chemotherapy, to ablate patient’s immune responsiveness and reduce tumor burden</td>
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<td>Institution of neutropenic mouth-care practices Xerostomia management secondary to anticholinergic medications for nausea Supportive care for ulcerative mucositis, xerostomia, pain, nausea Continued surveillance of neutropenic mouth-care practices GVHD management as needed</td>
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<tr>
<td>Stage III. Early engraftment to recovery of circulating counts (Days +22 to +100) Gradual reduction in risk from neutropenia, anemia, and thrombocytopenia</td>
<td>Risk for chronic GVHD</td>
<td>Ongoing supportive care per Stage II Introduction of conventional mouth-care protocols GVHD management as needed</td>
</tr>
<tr>
<td>Stage IV. Recovery of circulating counts to immune reconstitution (days +101 to +365) Anticipated immune recovery by 1 year post-transplant</td>
<td></td>
<td>Comprehensive oral care initiated when immune recovery permits Maintenance of optimal oral health over life span of patient</td>
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<tr>
<td>Stage V. Long-term survivorship (&gt;1 yr post-transplant) Monitor for evidence of relapse or secondary malignancies Monitor for growth and development sequelae (pediatric cohorts)</td>
<td></td>
<td>Maintenance of optimal oral health over life span of patient Monitor for evidence of relapse or secondary malignancies Management of craniofacial development abnormalities as needed</td>
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GVHD = graft-versus-host disease.
upper mantle head and neck radiation, can cause additional oral toxicities.

High-dose chemotherapy with or without stem cell rescue

Patients receiving these therapies typically experience ulcerative oral mucositis, dysgeusia, and xerostomia and are at risk for oral hemorrhage. In addition, allogeneic hematopoietic cell transplant patients may develop treatment-specific complications, including graft-versus-host-disease (GVHD).

Hematopoietic stem cell transplantation is generally used to treat acute myelogenous leukemia following remission induction or to treat other malignancies that have either failed to completely respond to conventional chemotherapy or that directly involve marrow (Figure 8–15). The transplant model can be discussed in the context of five stages (Table 8–3).

Oral mucositis

Severe ulcerative oral mucositis can result from high-dose chemotherapy or radiation to oropharyngeal tissues (Figure 8–16) (see Chapter 20). Etiology of the lesion is multidimensional and appears to include the following:

- direct injury to replicating basal epithelial cells by cytotoxic cancer therapy
- disturbances in mucosal immunity
- exacerbation of injury secondary to factors including metabolites produced by oral microflora
- wound-healing compromise secondary to infection and anemia

Mucositis causes significant pain, interferes with oral intake and other oral functions, and may be a port-

Table 8–4 Management of Oral Mucositis

<table>
<thead>
<tr>
<th>Degree of Mucositis</th>
<th>Initial Therapy</th>
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<tbody>
<tr>
<td>Mild</td>
<td>Bland rinses</td>
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<tr>
<td></td>
<td>0.9% normal saline</td>
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<tr>
<td></td>
<td>Sodium bicarbonate solution</td>
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<tr>
<td></td>
<td>Mucosal coating agents</td>
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<td></td>
<td>Antacid solutions</td>
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<td></td>
<td>Kaolin solution</td>
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<td></td>
<td>Water soluble lubricating agents, including artificial salivas</td>
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<table>
<thead>
<tr>
<th>Mild to moderate</th>
<th>Topical anesthetics</th>
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<tbody>
<tr>
<td></td>
<td>Viscous lidocaine</td>
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<tr>
<td></td>
<td>Dyclonine rinse or spray</td>
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<td></td>
<td>Benzocaine sprays or gels</td>
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<tr>
<td></td>
<td>Diphenhydramine solutions</td>
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<td></td>
<td>Hydroxypropyl cellulose film-forming agents (eg, Zilactin®)</td>
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<th>Moderate to severe</th>
<th>Opiate analgesics</th>
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<tr>
<td></td>
<td>Morphine: oral time-release, IV (bolus), patient-controlled analgesia</td>
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<tr>
<td></td>
<td>Fentanyl: patches</td>
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<td></td>
<td>Meperidine</td>
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more broad dosing of mucosal surfaces. Rinsing with topical anesthetics carries the risk of reducing the gag reflex, which can potentially result in aspiration pneumonia; this risk is elevated when the rinse is gargled. Risk associated with systemic absorption of anesthetics does not appear to be increased in the setting of ulcerated oral mucosa; however, swallowing anesthetics can result in systemic toxicity. Care should be taken when patients anesthetize their mouths prior to eating, for reasons including increased likelihood of accidental mucosal trauma that can in turn increase the probability of additional trauma and infection.

Topically administered agents have a relatively short duration of effect; therefore, it is important to introduce systemic analgesics as soon as pain management with the above agents is deemed insufficient. Opiates formulated for timed release via tablets, skin patches, or by computerized patient-controlled analgesia (PCA) methods are interventions of choice. Studies have clearly shown that PCA results in superior pain control with significantly fewer drug doses and side effects.

Research is currently delineating interventions designed to prevent or reduce oral mucositis caused by chemotherapy or radiation. Nonsteroidal anti-inflammatory drugs and members of the prostanoid family have shown beneficial effects in initial clinical trials. Of note, benzydamine hydrochloride, a topical anti-inflammatory agent that has also shown analgesic properties, has undergone extensive testing in the United States and is likely to be approved for use for mucositis management. Preventive or therapeutic efficacy of oral sucralfate suspension, which is intended to form a protective coat, is not clear, based on several conflicting studies. New strategies directed at enhancing mucosal immune function or promoting wound healing are currently being tested. Approaches currently under study include low-energy helium-neon laser, cytokines (e.g., epidermal growth factor, transforming growth factor-3, α-interferon, keratinocyte growth factor), and misoprostol (a prostaglandin analogue). Modification of oral microflora via administration of defensins also shows promise, based on early clinical trials. Moderation of oral mucositis by the administration of antioxidants has yet to be documented.

**Oral hemorrhage**

There are multiple reasons for oral hemorrhage in patients receiving cancer therapy, including thrombocytopenia, disseminated intravascular coagulation, hepatic disease, oral infection and mucosal trauma (Figures 8–17 and 8–18). Spontaneous mucosal petechiae and gingival bleeding typically occur at platelet levels of less than 20,000 to 30,000/mm$^3$. Oral bleeding can be of concern to patients and caregivers; pooling with whole saliva can give the appearance of more severe bleeding than actually exists.

Topical therapy should address formation of a stable clot and protection of the wound until initial

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**Figure 8–17**  
A, Submucosal bleeding of the palate in a thrombocytopenic cancer patient. Platelet count was approximately 35,000/mm$^3$.  
B, Submucosal bleeding causing purpuric lesions of the posterior pharyngeal wall, in a patient with chemotherapy-induced thrombocytopenia (blood platelets <20,000).  
C, Multiple areas of subepidermal bleeding causing widespread ecchymoses of the skin in a patient with acute myelogenous leukemia and low platelet count.
epithelialization has been established. Gauze soaked in topical thrombin can be applied directly to the bleeding site. Application of ice can enhance vasoconstriction; alternatively, drugs, such as topical cocaine solution or epinephrine, can be used. Agents designed to enhance clot formation (eg, microfibrillar collagen) may contribute to organization and stabilization of clots. Topical or systemic aminocaproic acid may also be of value. Platelet transfusions may be necessary, depending on severity of bleeding diathesis or tissue invasiveness of a procedure.

Salivary gland dysfunction
Intact salivary function is an important component of oral host defenses against infections. Patients with salivary gland dysfunction are thus at risk for infections of the mucosa, dentition, and periodontium. Head and neck radiation can affect salivary gland function (see Chapter 20). Degree of injury is directly proportional to exposure of salivary tissue to ionizing radiation. Glandular doses in excess of 2500 cGy typically produce limitations in saliva production, which at higher dosages may be irreversible. Thus, salivary changes are commonly observed in patients receiving head and neck radiation for squamous cell carcinoma, Hodgkin lymphoma or non-Hodgkin lymphoma. By comparison, degree of salivary gland dysfunction in patients receiving chemotherapy varies. Recovery of gland function generally occurs within several weeks following discontinuation of chemotherapy.

Patients receiving radiation or chemotherapy typically receive a variety of drugs in addition to chemotherapy, including antiemetics or antihistamines. Many of these medications exert anticholinergic effects, resulting in xerostomia. Mouth breathing or oxygen masks can lead to further dessication of oral tissues.

Management of salivary gland dysfunction is important for several reasons, including reduction of mucosal trauma and infection, and improved quality of life (see Chapter 26). Frequent oral rinses with normal (0.9%) saline can stimulate salivary gland function and promote mucosal hydration and oral hygiene. Commercially available artificial saliva may provide temporary symptomatic relief. Salivary gland function can be stimulated via sugarless gum or candies, or by medications that function as secretagogues. For example, pilocarpine hydrochloride directly stimulates salivary gland function and has been shown to be useful for managing xerostomia. Dietary interventions, including use of moist foods (eg, flavored gelatins) and sauces and gravies, can increase the comfort of eating. The type and texture of nutrients that are effective in enhancing food intake varies among patients. Taste bud viability also may play a role regarding appetite and interest in eating. Dry or cracked lips should be kept lubricated with agents such as lanolin-based creams and nonmedicated skin moisturizers.

Rapidly progressive dental caries can be a particularly significant oral complication in patients who develop chronic xerostomia following radiation therapy or who have developed chronic GVHD following stem cell transplantation. The carious lesions result from a combination of a loss of remineralizing elements provided by saliva, loss of antimicrobial proteins and substances found in saliva, and an ecologic shift to increasingly cariogenic bacterial flora. Patient compliance with comprehensive management is critical to minimizing risks associated with these changes. This includes effective dental plaque removal via brushing and flossing, diet modifications to reduce sucrose intake, daily application of stannous or neutral sodium fluorides, and topical oral antimicrobial rinses (eg, chlorhexidine or povidone iodine).

Neurotoxicity
Selected chemotherapeutic agents, notably the vinca alkaloids vincristine and vinblastine, can directly cause neurotoxicity. Symptoms include severe, throbbing pain that can mimic pain secondary to dental disease, includ-
ing irreversible pulpitis. Diagnosis is usually made by exclusion of more overt causes of dental, periodontal, or muscular origin. Opioid-containing analgesics are often effective for pain relief. The lesion generally dissipates over several weeks following discontinuation of the causative chemotherapeutic agent.

Chemotherapy patients may also develop a transient, mild to moderate dental hypersensitivity within weeks following initiation of chemotherapy. Although the etiology is not well understood, symptoms generally are responsive to topical application of fluorides or desensitizing toothpaste. The condition generally resolves several weeks after discontinuation of chemotherapy.

Patients receiving chemotherapy or head and neck radiation may also develop dysgeusia. The lesion apparently develops in the setting of disrupted regeneration of taste buds coupled with xerostomia that reduces delivery of taste stimulants to the taste bud receptors themselves. Olfactory disturbances can exacerbate dysgeusia. Also, cancer chemotherapy can occasionally diffuse into the oral cavity, thereby producing an offensive taste; this process is termed venous taste phenomenon.

Bruxism or clenching may develop in cancer patients owing to stress, sleep dysfunction, or selected medications that cause CNS toxicity. Temporomandibular dysfunction (TMD) can ensue; facial pain or headache are predominant symptoms. Management directed to underlying causative factors may include anxiolytics or muscle relaxants. Physical therapy, including moist heat applications, massage, and gentle stretching may also be effective. Patients with nocturnal bruxism may benefit from wearing customized occlusal splints while sleeping.

Alterations in craniofacial growth and development
High-dose chemotherapy can damage developing dental and skeletal structures in children and adolescents. Addition of radiation to treatment protocols (eg, cranial radiation for leukemia or total body irradiation for marrow transplants) significantly increases propensity for damage to developing teeth. Most severe effects are observed in patients treated for malignancy at ages younger than 5 years. Dental abnormalities include hypoplastic dentin and enamel, tooth crown discoloration, blunted or conical root formation, taurodontism, and diminutive teeth. Complete agenesis of teeth can occur in severe cases. Dental eruption can be compromised secondary to altered tooth development as well as disturbances in alveolar, mandibular, and maxillary osseous growth. These changes often produce the need for orthodontic or cosmetic management.

Second primary neoplasms
Second primary cancers are well recognized as potential complications for long-term survivors of high-dose chemotherapy and radiation therapy for cancer (Figure 8–19). Incidence rate for marrow transplant recipients ranges between 1% and 2%. In a study by the Seattle transplant group, the majority (63%) of the second malignancies associated with marrow transplant were hematologic malignancies (eg, non-Hodgkin lymphoma following treatment for leukemia) whereas 37% represented a wide variety of solid tumors. Skin and mucosal carcinomas are the most commonly diagnosed secondary solid tumors, including oral squamous cell carcinomas.

Graft-versus-host disease
Graft-versus-host disease most commonly occurs in allogeneic transplant recipients, although a clinically similar lesion mimicking acute GVHD can also develop in autologous transplant patients. Specific target tissues include skin, liver, lacrimal glands, and oral mucosa and salivary glands (Figure 8–20). Reasons for this distribution are not well-defined. The process is principally mediated via cytotoxic T cells present in the graft that react against host tissue. The basis for autoreactivity in autologous GVHD is less well understood than for allogeneic GVHD. Matching of patient and donor for major histocompatibility loci (eg, human leukocyte antigen) is a primary means of reducing risk for development of GVHD. Disparities at minor histocompatibility loci partially govern clinical expression as well.

Acute GVHD occurs between days 14 and 100 post-transplantation and is usually more limited in severity than chronic GVHD. Chronic GVHD classically occurs between days 100 and 500 post-transplantation and involves multiple organs. A given patient may develop either acute or chronic GVHD, or progress from acute to chronic forms. Graft-versus-host disease can be fatal, infection being a principal cause of death.

Immunosuppressive drugs are used prophylactically in allogeneic patients to reduce development of acute GVHD. Cyclosporine, methotrexate, prednisone, or FK-506 alone or in combination are drugs of choice for
BLOOD DYSCRASIAS

with lesions at other sites. Systemic treatment includes high-dose immunosuppressive therapy with combination high-dose prednisone and cyclosporine. Steroid rinses, creams, ointment-pastes, or gels applied directly to the oral mucosal ulcerative lesions may promote healing by reducing inflammation. Ongoing maintenance of optimal oral hygiene is important in context of reducing risk for oral infection in the setting of dysregulated mucosal immune systems. Topical administration of cyclosporine or psoralen-ultra violet A (PUVA) intraoral therapy may also be of benefit, although further research is needed. Therapy continues until the GVHD subsides and graft tolerance occurs.

Both GVHD and its prophylaxis and treatment are immunosuppressive and significantly increase risk for infection. Active periodontal disease and dental infections should be eliminated. Patients should perform comprehensive oral hygiene practices, especially when receiving high-dose immunosuppressive therapy. Atypical presentations of recurrent herpes simplex and other viral infections as well as candidiasis can occur. Appropriate antimicrobial agents are frequently required as adjunctive treatment. Clinical vigilance is essential for prompt diagnosis so that treatment can be immediately instituted.

Suggested reading