

Children with Leukemia

Because of increasing survival rates for children with ALL and the extensive side effects of the treatments, the therapist must pay attention to specific measures of cognition, function, activity, and participation when planning an appropriate intervention program. All components are needed in a comprehensive program.¹¹⁹

Short- and long-term impairments can affect any or all of these components. Decreased Hb levels, osteonecrosis, joint range of motion, strength, gross and fine motor performance, fitness, and attendance or absence from school are all factors to consider.¹¹⁹

Long-term effects of treatment and CNS prophylaxis can include peripheral neuropathies, neuropsychologic disorders, problems with balance, decreased muscle strength, and obesity. CNS prophylaxis includes intrathecal chemotherapy (injection of drugs into the spinal fluid) and cranial irradiation. Cranial irradiation and obesity are significant predictors of impaired balance.²⁰²

Preschool children with immature nervous systems may be more sensitive to the neurotoxicity of radiation and chemotherapy, placing them at a greater risk for CNS damage than children with fully developed neurologic systems.¹²⁴ Learning difficulties, cognitive deficits, attention problems, and lack of participation in physical activities can be sequelae of medical treatment.²⁰²

Personal factors such as a family's cultural belief system may influence how children and their parents perceive rehabilitation and specific interventions. Health-related quality of life and goals may be driven by family and cultural values that are not necessarily what the therapist perceives as in the best interest of the child's function and fitness.

The therapist should try to match the program with the family's cultural expectations, ability to participate, and emotional and financial resources. Expecting from the family only what they can succeed at and providing support and education where they are needed to help the family grow and care for their child with medical needs will create the best therapeutic environment for the child to thrive in.

Malignant Lymphomas

Lymphoma is a general term for cancers that develop in the lymphatic system. Lymphomas are divided into two groups: Hodgkin's lymphoma (HL; also known as Hodgkin's disease) and non-Hodgkin's lymphoma (NHL). With the extensive progression in cytogenetic research that has occurred over the past 5 years, this distinction is beginning to obscure.

It is becoming more useful to categorize lymphomas according to their clinical behavior—indolent or aggressive—and their chromosome features. Currently HL is distinguished from other lymphomas by the presence of a characteristic type of cell known as the Reed-Sternberg cell. All other types of lymphoma are called NHL.

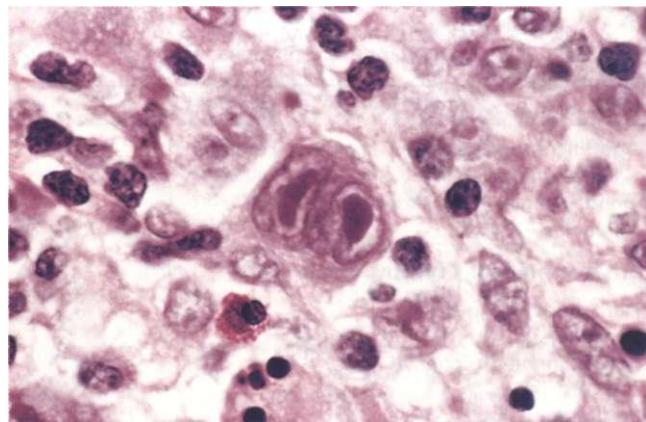


Figure 14-6

Reed-Sternberg cell. Named for Dorothy M. Reed, American pathologist (1874-1964) and Karl Sternberg, Austrian pathologist (1872-1930). This is one example of the large, abnormal, multinucleated reticuloendothelial cells in the lymphatic system found in HD. The number and proportion of Reed-Sternberg cells identified are the basis for the histopathologic classification of HD. (Reprinted from Kumar V, Cotran RS, Robbins SL: *Basic pathology*, ed 6, Philadelphia, 1997, WB Saunders. Courtesy Dr. Robert W. McKenna, University of Texas Southwestern Medical School, Dallas.)

Hodgkin's Lymphoma

Definition and Overview. HL is lymphoid neoplasm with the primary histologic finding of giant Reed-Sternberg cells in the lymph nodes. These cells are part of the tissue macrophage system and have twin nuclei and nucleoli that give them the appearance of owl eyes (Fig. 14-6).

Although this malignancy originates in the lymphoid system and primarily involves the lymph nodes, it can spread to other sites such as the spleen, liver, bone marrow, and lungs. There are two subtypes of HL: classic HL (further divided into the categories of nodular sclerosing HL, mixed-cellularity HL (MCHL), lymphocyte-rich classic HL, and lymphocyte-depleted HL) and nodular lymphocyte-predominant HL (LPHL). LPHL is uncommon and represents only 4% to 5% of HL cases.

Incidence and Risk Factors. Classic HL can occur in both children and adults but peaks at two different ages: between the ages of 25 and 30 years and after the age of 55 years. Children younger than 5 years rarely develop this disease, while only 10% of HL cases occur in children 16 years old and younger. LPHL typically has only one peak incidence around the fourth decade. Approximately 7800 cases of HL are diagnosed in the United States each year (typically men more than women).⁹¹

Although the exact cause of HL remains under investigation, certain risk factors have been identified (Table 14-4). One factor that has been related to HL is previous infection with EBV. The DNA of this virus has been found in the Reed-Sternberg cells of about 50% of clients with classic HL (about 90% in developing countries).

Pathogenesis. HL is a B-cell-type malignancy with clonal expansion of a malignant B cell. The reason for the transformation from a normal B cell to a malignant cell is still under investigation, but significant progress has

Table 14-4 Risk Factors for Malignant Lymphomas

NHL	HL
Age (increased risk with increasing age)	Familial
Gender (males more than females)	
Environmental Contaminants	
Herbicides and pesticides (?)	
Benzene (?)	
Polychlorinated biphenyls (PCBs) (?)	
Radiation	
Viral Infection	
EBV, mononucleosis virus	EBV, mononucleosis virus
Human T-Lymphotropic virus type I (HTLV-1)	
HIV	
Congenital Immunodeficiency Syndromes	
Hepatitis C (?)	
Immunocompromise/immunodeficiency	
Chronic disease or illness; autoimmune diseases	Chronic disease or illness; autoimmune diseases
Immunosuppressants	Immunosuppressants
Cancer treatment with alkylating or cytotoxic agents	Cancer treatment with alkylating or cytotoxic agents
Inherited immune deficiencies (e.g., collagen vascular disease)	SLE
HIV	HIV
AIDS	AIDS
<i>Helicobacter pylori</i> bacteria (gastric lymphoma)	Ulcerative colitis
Methotrexate	Drug abuse
Obesity (women)	Obesity (men)

been made. Recent evidence suggests that an infection or inflammation may be involved. As just discussed, genes from EBV are found in half of all HL cases in the industrialized world.

Products from these genes (*LMP1*, *LMP2*, and *EBNA1*) have the ability to mimic transmembrane receptors and activate the transcription factor NF-KB (which is normally inhibited). NF-KB, through its function of regulating dozens of genes within the cell, plays a key role in the proliferation and survival of the malignant clones. The products of these genes include cytokines and chemokines.

Many cytokines, particularly interleukins, are involved in producing an environment where the Reed-Sternberg cells thrive. For example, some interleukins attract inflammatory cells (eosinophils, monocytes, and mast cells), which aid in the survival of the cell. In the laboratory, if these inflammatory cells are not surrounding the Reed-Sternberg cells, they do not survive.

Other interleukins expressed by the Reed-Sternberg cells inhibit the activation of T cells, which normally

destroy abnormal cells. This inhibition creates an area of local immunosuppression and allows the Reed-Sternberg cell to evade detection. Some interleukins act as growth factors, encouraging proliferation, metastasis, and angiogenesis. Another protein induced by NF-KB, termed c-FLIP, is incorporated into a complex that signals cell death but is not functional in that capacity, thereby evading apoptosis and making the cell immortal.²⁹

Reed-Sternberg cells also express receptors for receiving signals from inflammatory cells, creating "cross-talking" between the malignant cells and surrounding inflammatory cells, which may contribute to the ability of the Reed-Sternberg cells to metastasize.

Clinical Manifestations. See Fig. 14-7.

Classic HL and LPHL present with different clinical manifestations and progression of disease. Because of these distinctions, these two subgroups are discussed separately.

Classic Hodgkin's Lymphoma. Classic HL begins in a group of lymph nodes and spreads contiguously to other lymph node chains. The cervical, axillary, and para-aortic lymph nodes and mediastinum are the most common initial locations for involvement (Fig. 14-8). These lymph nodes are typically nontender and firm.³¹

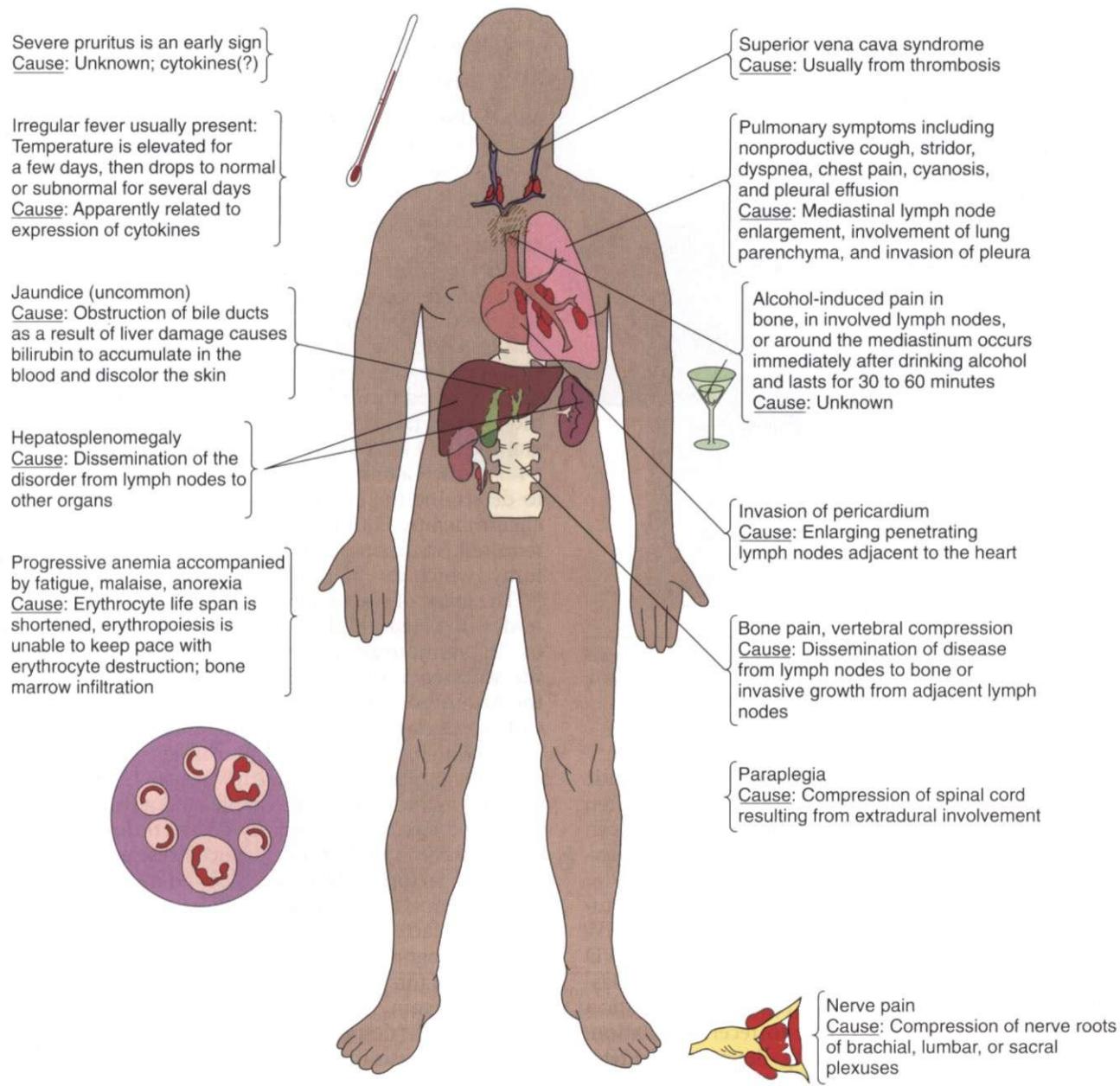
Nodular sclerosing HL typically presents with supradiaphragmatic lymph node involvement, while MCHL often exhibits smaller involved lymph nodes in a subdiaphragmatic location or involves organs. Clients who have disease below the diaphragm, MCHL, or "B" symptoms are more likely to develop splenic involvement. Splenic involvement is seen in 30% to 40% of people with HL, but detection is often difficult. An enlarged spleen does not necessarily indicate involvement, while a normal size spleen does not rule out involvement. HL in the liver is rare and seen only with splenic involvement.³¹

Bone marrow involvement occurs in less than 10% of newly diagnosed cases. If lymph nodes become large and bulky, they can lead to further symptoms, such as tracheal or bronchial compression (with accompanying shortness of breath) or obstruction of the GI tract. Lymph nodes may grow and enlarge and finally perforate the lymph node capsule, continuing to grow and invade into adjacent tissue or organs. This can occur in the lung, pericardium, pleura, chest wall, gut, or bone.³¹

Effusions (collections of fluid) may also develop in the lung, heart, or abdominal cavity. Tumor can spread not only from lymph node to adjacent lymph node, but via the bloodstream to lung, liver, bone marrow, and bone. Involvement in these areas is often indicative of extensive disease. As bone marrow is replaced, infections, anemia, and thrombocytopenia result.³¹

Primary involvement of the CNS is rare, and dissemination of disease to the CNS is uncommon.³¹ Occasionally spinal cord involvement may occur in the dorsal and lumbar regions, and compression of nerve roots of the brachial, lumbar, or sacral plexus can cause nerve root pain. Epidural involvement (also uncommon) causes back and neck pain with hyperreflexia. Extremity involvement is characterized by pain, nerve irritation, and obliteration of the pulse.

A significant number of people (25%) present with "B" symptoms. The fever associated with HL is intermittent

**Figure 14-7**

Pathologic basis for the clinical manifestations of HD.

and occurs with drenching night sweats. Clients may also complain of fatigue, pruritus, and pain associated with drinking alcohol.

Lymphocyte-PredominantHodgkin'sLymphoma. LPHL typically presents with one-node involvement rather than groups of involved lymph nodes. This occurs in peripheral lymph nodes such as the cervical, axillary, or inguinal lymph node chains. Unlike classic HL, LPHL does not follow an orderly pattern of spread, but can be found in lymph nodes distant from the original node of disease. LPHL infrequently involves the bone marrow, spleen, or thymus. "B" symptoms rarely occur. LPHL has an indolent clinical course with long disease-free intervals. Relapse is common but responds well to treatment.¹⁴⁸

Special Problems

Pregnancy and Hodgkin's Lymphoma. Since the mean age at diagnosis of HL is 32 years, it is not uncommon for women to develop HL while pregnant. Diagnostic staging can be accomplished safely with magnetic resonance imaging (MRI) because it does not use ionizing radiation¹⁴⁹; it has no adverse impact on the natural course of HL; and HL has no effect on the course of gestation, delivery, or the incidence of prematurity or spontaneous abortions. The risk of metastatic involvement of the fetus by HL is negligible.⁶²

The management of HL during pregnancy must be individualized. Many women have been successfully treated while pregnant without adverse effects on the fetus.⁶³ In cases of disease onset early in pregnancy, the



Figure 14-8

Enlarged cervical lymph node associated with HD. (Reprinted from del Regato J, Spijut HJ, Cox JD: *Cancer: diagnosis, treatment, and prognosis*, ed 6, St Louis, 1985, Mosby-Year Book.)

recommendation may be made to consider a therapeutic abortion. Women presenting in later pregnancy are often able to have therapy delayed until after delivery or can undergo modified or standard combination chemotherapy and radiation therapy.⁶²

Antiretroviral treatment and prophylaxis for opportunistic infection may also be administered for HIV-positive women.¹⁰² With the increased use of ABVD therapy (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine) and reduced reliance on radiation therapy, most women do not have to receive radiation. However, with appropriate shielding, the estimated fetal dose of radiation can be reduced by 50% or more in most cases if required.⁷³ In nonpregnant women, to further reduce any risk, it is advisable to delay pregnancy for 12 months after completion of radiation therapy.⁶³

Long-term semen banking is available for men whose future fertility may be compromised by suppression of spermatogenesis secondary to administration of chemotherapy or radiotherapy treatment. Banking of a single ejaculate before chemotherapy or radiotherapy treatment may preserve potential fertility without compromising the oncology treatment.⁸³

Hodgkin's Lymphoma in AIDS. Although HL does not occur as frequently in HIV-positive clients as does NHL, people with HIV are still at increased risk of developing HL (about eight- to tenfold increase). When it occurs, the histology is usually MCHL associated with aggressive, disseminated disease and systemic symptoms. Since the introduction of highly active antiretroviral therapy (HAART), the incidence of HL in clients with HIV has not changed significantly, but there has been an improve-

ment in mortality rate, particularly due to the HAART therapy and reduced AIDS-related deaths.⁶⁷

MEDICAL MANAGEMENT

DIAGNOSIS AND STAGING. Diagnosis depends on identification of Reed-Sternberg cells in lymph node tissue or at other sites that exhibit the characteristic markers of CD15+ and CD30+. This can often be achieved by excisional biopsy (needle biopsy usually does not provide enough cells for diagnosis since only 2% to 3% of the cells in a lymph node are malignant) of involved tissue (usually an accessible lymph node). Biopsied tissue is examined under the microscope for Reed-Sternberg cells and tested for markers using immunohistochemistry.

Once the diagnosis is made, staging of the disease is accomplished through a complete physical examination; blood tests (sedimentation rate); and computed tomographic (CT) scan of the chest, abdomen, and pelvis (Fig. 14-9). Often a bone marrow biopsy or aspirate is needed to determine the extent of the disease. Because systemic chemotherapy is utilized, extensive staging is no longer required, including exploratory laparotomy or splenectomy (which can be more dangerous than helpful).

The stage of the neoplasm depends on the number of nodes involved, the location of the nodes, the presence of "B" symptoms (fever, weight loss, night sweats), the sedimentation rate, and size of nodes. Staging is by the Ann Arbor system or the modified version called the Cotswolds classification, denoting stages I to IV (see Table 14-6), which helps determine treatment.

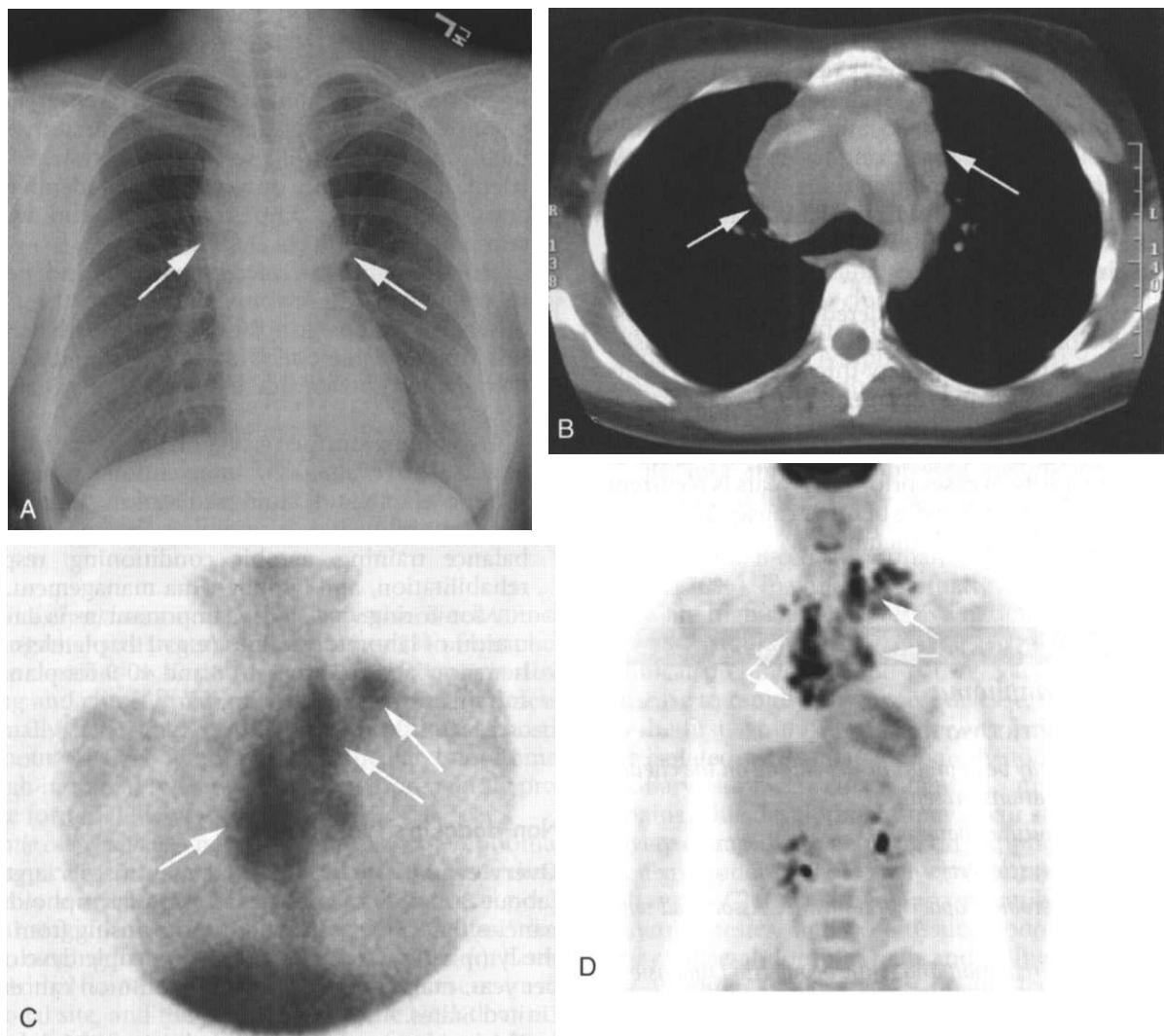
Three prognostic groups have also been proposed: early favorable, early unfavorable, and advanced disease. Advanced disease is further divided according to the presence of seven risk factors: advanced disease plus zero to three risk factors is staged as advanced disease with favorable prognosis, and advanced disease with greater than three risk factors is termed advanced disease with unfavorable prognosis.⁷⁷

Some factors denoting a worse prognosis include a low serum albumin, low hemoglobin, age over 45 years, and male gender (despite stage). Other factors that carry a poorer prognosis include "B" symptoms, stage IV disease, too high or too low lymphocyte count, or high WBC count. These factors are often considered in subsequent treatment options.

TREATMENT. Cure of HL is the primary treatment goal through the use of chemotherapy and, in some cases, both chemotherapy and radiation. The specific treatment is guided by the stage of the disease at diagnosis. The combination chemotherapy of choice is ABVD. Seventy-five percent of clients are cured with this treatment (with or without radiation).

Persons classified as having early favorable disease (stage IA or IIA) receive either four courses of ABVD or two courses of ABVD plus involved-field radiation treatment. Early unfavorable disease (stage IA, IB, IIA, HB, a large mass in the chest, or other unfavorable characteristics) is typically treated with four courses of ABVD plus involved-field radiation treatment.

Advanced disease (stages III and IV) with favorable prognosis treatment includes six courses of ABVD.

**Figure 14-9**

HD as seen on chest radiograph (**A**); CT scan of the chest (**B**); gallium scan of the head, neck, and chest (**C**); and PET scan (**D**). The arrows indicate sites of disease. Note that PET and CT scans provide more detailed information compared with chest radiograph and gallium scan. (Reprinted from Goldman L: *Cecil textbook of medicine*, ed 22, Philadelphia, 2004, WB Saunders.)

Advanced disease with unfavorable prognosis can be treated with aggressive combination chemotherapy using BEACOPP (bleomycin, etoposide, Adriamycin [doxorubicin], cyclophosphamide, vincristine, procarbazine, prednisone) or Stanford V (with or without radiation). Other therapies are available for advanced disease; all have significant toxicities and varying effectiveness.⁵⁰⁻⁶⁹

As therapy progresses, some oncologists are utilizing positron emission tomography (PET) scans to determine the effect of treatment. For example, if a large mass in the chest of a child shrinks significantly with chemotherapy, radiation can be avoided. PET and gallium scans (a nuclear medicine scan) are also used to determine if there is any residual disease upon completion of therapy.

For people with relapsed HL after combination chemotherapy or for those clients with disease that did not completely respond to treatment (10% to 15%), current data support the use of high-dose chemotherapy with

autologous stem cell or peripheral blood stem cell transplantation. Biologic treatments such as monoclonal antibody-based therapies (e.g., rituximab) are still being investigated,⁶⁰ while new efforts are being made to develop drugs that could inhibit genes or protein products that contribute to the pathogenesis of HL.

Current treatments are being evaluated for long-term toxicity since the survival rate has improved. ABVD is associated with a long-term risk of less than 1% for developing acute leukemia, while radiation (mantle and para-aortic fields) has a 1% per year lifetime risk of developing a solid tumor in smokers and 0.5% in nonsmokers. The most common solid tumors noted include lung and breast cancers.^{47,113}

Those who survive HL have a 13% risk of developing a solid tumor at 15 years that increases to 22% at 25 years of survival (this increase does not appear to plateau).⁵⁴ Clients who received radiation to the chest also have a

higher risk of fatal myocardial infarction (presumed to be caused by damage to the intimal lining of the coronary arteries).

ABVD has not been shown to cause infertility in men or women, as do the older alkylating agents previously used. Because of the increased long-term complications, the use of radiation has been limited to only areas in field and lower doses are being used, particularly in children. The combination therapy of ABVD appears to be a better long-term choice for treatment.¹⁴

PROGNOSIS. HL is now considered one of the most curable forms of cancer, and death rates have decreased 60% since the early 1970s. Ninety-three percent of clients are alive at 1 year following treatment. The 5-year survival rate is about 85%, while the 10-year rate is 78%. At 15 years and beyond, the relative rate is 68%. The cause of death in the majority of cases prior to 15 years is recurrent disease. After 15 years, most die of other causes, including neoplasms derived from HL therapy.

SPECIAL IMPLICATIONS FOR THE THERAPIST

14-7

Hodgkin's Lymphoma

PREFERRED PRACTICE PATTERNS

Other patterns may be appropriate depending on the client's age and complications present.

4B: Impaired Posture (bone pain)

4C: Impaired Muscle Performance

6B: Impaired Aerobic Capacity/Endurance Associated with Preconditioning

6H: Impaired Circulation and Anthropometric Dimensions Associated with Lymphatic System Disorders

7A: Primary Prevention/Risk Reduction for Integumentary Disorders (lymphedema; edema)

The therapist may palpate enlarged, painless lymph nodes during a cervical, spine, shoulder, or hip examination. Lymph nodes are evaluated on the basis of size, consistency, mobility, and tenderness. Lymph nodes up to 2 cm in diameter, soft consistency, freely and easily moveable, tender to palpation, and transient are considered within normal limits but must be followed carefully.

Lymph nodes greater than 2 cm in diameter that are firm in consistency, nontender to palpation, fixed, and hard are considered suspicious and require evaluation. Enlarged lymph nodes associated with infection are more likely to be tender than slow-growing nodes associated with cancer.

Changes in size, shape, tenderness, and consistency should raise a red flag. The physician should be notified of these findings and the client advised to have the lymph nodes evaluated by the physician; in someone with a history of cancer, immediate medical referral is necessary.

The therapist's role in lymphoma includes, but is not limited to, assessing and/or addressing (1) quality of life issues, including emotional and spiritual needs; (2) impairments, functional limitations, and

disabilities; and (3) physical conditioning and deconditioning.

Generalized weakness, decreased endurance, impaired mobility, altered kinesthetic awareness and balance, including unstable gait; respiratory impairment; involvement of the lymphatic system (lymphedema); and pain are only a few of the identified signs and symptoms of impairment common with this group of people.

Requirements for infection control and treatment subsequent to the cytotoxic effects on the CNS are outlined previously in the section on the leukemias. Additionally, side effects of radiation and/or chemotherapy must be considered (see Chapter 5 and Table 9-8).

Depending on the results of the therapist's examination and evaluation, intervention strategies may include client and family education, pain management, mobility and gait training, therapeutic exercise, balance training, aerobic conditioning, respiratory rehabilitation, and lymphedema management.

Monitoring vital signs is important, as is daily evaluation of laboratory values (e.g., Hb, platelets, WBCs, hematocrit). See Tables 40-8 and 40-9 for planning or carrying out a therapy program.¹⁷

Non-Hodgkin's Lymphomas

Overview and Incidence. NHL comprises a large group (about 30 specific types described) of lymphoid malignancies that present as solid tumors arising from cells of the lymphatic system. Over 67,000 people develop NHL per year, making it the fifth most common cancer in the United States.

The incidence rate has doubled since 1970, in part due to the increase in HIV-related disease, but the reasons for the remaining cases are unknown. Most of the increase has been noted in women, but NHL is still more common in men. Ninety-five percent of NHL occurs in adults and only 5% develop in children; yet the types of NHL in adults are different than those seen in children. The average age of onset in adults is between 60 and 70 years.

The lymph nodes are usually involved first, and any extranodal lymphoid tissue, particularly the spleen, thymus, and GI tract, may also be involved. The bone marrow is commonly infiltrated by lymphoma cells, but this is rarely the primary site of a lymphoma.

Lymphomas are classified according to the Revised European/American Lymphoma/WHO system, which relies on the histochemical, genetic, and cytologic features. Lymphomas are classified as either B cell or T cell. B-cell lymphomas are more common than T-cell lymphomas.

The clinical course for each of the NHLs, even subtypes, is variable. The most common lymphoma is diffuse large B-cell lymphoma (DLBCL), which comprises 33% of all NHLs. It is an aggressive, fast-growing tumor. Studies have demonstrated three subtypes with different response rates and prognosis.

Box 14-6**ANN ARBOR STAGING CLASSIFICATION FOR HD**

Stage I:	Involvement of a single lymph node, group of nodes, or a single extralymphatic site I _E (e.g., spleen, thymus, Waldeyer's tonsillar ring) except liver and bone marrow
Stage II:	Involvement of two or more lymph node regions on the same side of the diaphragm or an extralymphatic site and its regional lymph nodes with or without other lymph nodes on the same side of the diaphragm
Stage III:	Involvement of lymph node regions or structures on both sides of the diaphragm; may include spleen or localized extranodal disease
Stage IV:	Widespread extralymphatic involvement (liver, bone marrow, lung, skin)

*For all stages: A = asymptomatic; B = constitutional or systemic symptoms.

Burkitt's lymphoma is a highly aggressive B-cell tumor requiring intensive treatment; only 1% to 2% of lymphomas are classified as Burkitt's. *Follicular lymphoma* is slow growing and clinically indolent (slow growing, painless, continually relapsing). Follicular lymphomas constitute about 14% of lymphomas. Follicular lymphoma, although indolent, may transform to a more rapidly progressive form, DLBCL.

Mantle cell lymphoma makes up only 2% of lymphomas but is typically widespread at diagnosis. Although these cells grow at an intermediate rate, the prognosis is poor. Clinical staging of NHL is according to the Ann Arbor system, ranging from stage I to stage IV (Box 14-6). Compared with HL, NHLs are more likely to present in an extranodal site, and the progression of the NHL does not follow the orderly anatomic progression from one lymph node to the next. Stage I and II NHLs are uncommon because the disease is much more likely to be disseminated at the time of diagnosis.

Etiologic and Risk Factors. Studies in the 1990s linked NHL to two widespread environmental contaminants: exposure to *benzene*, which originates from cigarette smoke, gasoline, automobile emissions, and industrial pollution, and *polychlorinated biphenyls* (PCBs) found throughout the food chain (highest in meats, dairy products, and fish).⁷⁶

One large study was unable to confirm the connection of benzene to lymphoma.²⁰⁰ Of benzene exposure that occurs in the environment, 70% is derived from vehicle exhaust emissions. The increase of environmental benzene has closely paralleled the rise in frequency of hematologic malignancies.¹³⁶

In people with HIV, the risk of developing NHL is significantly elevated compared with noninfected people. Other predisposing risk factors for lymphoma are listed in Table 14-4.¹⁴⁴

A wide variety of primary and secondary immunodeficiencies have been associated with an increased incidence of lymphomas. This phenomenon may reflect a decrease in the host's surveillance mechanism against transformed cells or be from prolonged exposure to

oncogenic agents, such as EBV, as a consequence of failure to mount an adequate immune response. The presence of *Helicobacter pylori* (bacteria) in the stomach lining is associated with the development of gastric lymphoma, but this comprises a very small proportion of cases. Low-dose methotrexate therapy used for classic and juvenile RA carries an increased risk of lymphoproliferative disease.^{23,42}

Pathogenesis. Although the exact cause of NHL is unknown, studies using techniques of molecular biology have provided some clues to the pathogenesis. The malignant lymphomas develop from the malignant transformation of a single lymphocyte that is arrested at a specific stage of B- or T-lymphoid cell differentiation and begins to multiply, eventually crowding out healthy cells and creating tumors, which enlarge lymph nodes.

Because immunosuppressed people have a greater incidence of the disease, an immune mechanism is suspected. Unlike in HL, T-cell function is minimally affected (30%), but B-cell abnormalities are more common in NHL (70%). In children, virtually all malignant lymphomas are high-grade, aggressive neoplasms.

Clinical Manifestations. The NHLs are variable in clinical presentation and course, varying from indolent disease to rapidly progressive disease. Lymphadenopathy is the first symptom of NHL, with painless enlargement of isolated or generalized lymph nodes of the cervical, axillary, supraclavicular, inguinal, and femoral (pelvic) chains. This development may occur slowly and progressively or rapidly depending on lymphoma type.

Extranodal sites of involvement may include the nasopharynx, GI tract, bone (accompanied by bone pain), thyroid, testes, and soft tissue. Abdominal lymphoma may cause abdominal pain and fullness, GI obstruction or bleeding, ascites, back pain, and leg swelling.

Lymph node enlargement in the chest can lead to compression of the trachea or bronchus, causing shortness of breath and coughing. Development of the superior vena cava (SVC) syndrome can occur secondary to compression of the SVC by enlarged nodes; this causes edema of the upper extremities and face. SVC syndrome is life threatening and requires immediate attention.

NHL presenting as polyarthritides has been reported, and Sjogren's syndrome is associated with malignant lymphomas.^{59,191} Constitutional symptoms include fever, night sweats, pallor, fatigue, and weight loss; when present, these systemic B symptoms typically predict a poor prognosis.

Primary CNS lymphoma is an NHL restricted to the nervous system. Presenting symptoms may include headache, confusion, seizures, extremity weakness/numbness, personality changes, difficulty speaking, and lethargy. Prior to the spread of HIV, this type of lymphoma was rare.

HIV and NHL. NHL is more common in clients with HIV than is HL and is an AIDS-defining illness. Typically lymphomas that occur in clients with HIV are aggressive, fast-growing tumors. The two major subtypes of lymphomas are CNS and systemic lymphomas (with or without CNS involvement).

Two rare lymphomas seen more frequently in people with HIV are primary effusion lymphoma and plasma-

blastic lymphoma of the oral cavity, but the most common types are DLBCL and Burkitt's lymphoma. Tumor is frequently diffusely spread at the time of diagnosis, with extranodal involvement common.

As discussed above, many illnesses that are accompanied by a reduced immune system demonstrate an increased incidence of NHL. Prior to aggressive HIV therapy (i.e., HAART), lymphomas in persons with HIV were associated with a very poor prognosis.

Currently the use of HAART has significantly reduced the risk of developing NHL and also improved tolerance for chemotherapy once diagnosed with NHL. This reduction is based on higher CD4 counts and improving the immune system. It appears that if HAART therapy is not effective, people with AIDS still have the same increased risk of developing NHL.¹¹¹ The improved immune status derived from HAART has increased treatment options for HIV-related lymphoma. Clients are now treated with the intent to cure, receiving chemotherapy, immune modulators, and BMT.

MEDICAL MANAGEMENT

DIAGNOSIS. Accurate diagnosis is important because of the other clinical conditions that can mimic malignant lymphomas (e.g., infection, tuberculosis, SLE, lung and bone cancer). Molecular genetic techniques that take advantage of the clonal nature of this malignancy are now being applied to better characterize and diagnose the lymphomas. However, at the present time a biopsy is still required to confirm the underlying cause of persistent enlargement of lymph nodes present on clinical examination.

CT scans of the chest, abdomen, and pelvis are helpful in staging, while MRI is used to image the brain and spinal cord. Bone marrow may be examined for staging and peripheral blood may be tested, but blood abnormalities are not present until the disease is in an advanced stage. If clinical symptoms warrant, a lumbar puncture for spinal fluid may be performed. Immunohistochemistry, flow cytometry, or cytogenetic testing is often done to distinguish one type of NHL from another.

The gallium scan (Ga scan, scintigraphy) using radio-tracer (gallium-67) uptake is 85% to 90% accurate to predict residual disease after chemotherapy and is able to differentiate between active tumor tissue and fibrosis (uptake only occurs in viable lymphoma tissue, not in fibrotic or necrotic tissue). PET imaging is becoming more widespread and can be performed to aid in the initial diagnosis and help ascertain if a lymph node is malignant or benign. PET is also used following chemotherapy (frequently along with CT) to determine if the lymphoma is reduced in size and the treatment is effective.

TREATMENT. Treatment varies for NHL depending on the type. In general, fast-growing tumors can be cured but require aggressive treatment. Slow-growing tumors often cannot be cured, but the clinical course is chronic and therapy is often reserved until symptoms develop, such as for follicular lymphoma. Localized disease (stage I or II) may be treated with radiation, whereas disseminated disease requires radiation and chemotherapy.

The most common chemotherapy combination is CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Another combination omits the doxorubicin (because of its effects on the heart) and is called CVP. Other agents include chlorambucil, fludarabine, and etoposide. Since many risk factors for NHL are associated with a reduced immune system, immune modulators, such as interferon and monoclonal antibodies, have been employed to combat NHL.

Combining the monoclonal antibody rituximab (Rituxan) with chemotherapy (CHOP) has produced high rates of response and is the treatment of choice for many NHLs, including DLBCL.⁴¹ Clinical studies suggest that the immune modulator rituximab may alter the sensitivity of B-cell lymphoma to chemotherapy as well as induce apoptosis and cause the lysis of B cells.

BMT may be used for clients who relapse or do not completely respond to treatment (which often occurs with aggressive lymphomas). Combined with intensive chemotherapy, BMT (autologous or allogeneic) can be curative. In 2002, 4300 transplants were performed. One fourth of these were allogeneic, while the remainder was autologous. Nonmyeloablative (i.e., the doses of chemotherapy are not high enough to ablate the bone marrow) transplants can be performed for older clients who normally cannot tolerate high-dose chemotherapy, but graft-versus-host complications are problematic.

For some lymphomas, chemotherapy becomes palliative because of an inability to overcome drug resistance within the lymphoma cells; attempts at overcoming specific drug resistance mechanisms have had limited success. Other strategies involve the use of antigen-presenting cells for taking up, processing, and presenting tumor protein in a vaccine strategy. This may provide a new immune mode to eradicate lymphoma, particularly tumor cells that persist following therapy.^{33,110}

Radioimmunotherapy, radioactive labeling of a monoclonal antibody, is also under investigation to provide targeted therapy and provide tumor-free grafts for transplant.^{19,197}

The optimal management of women with NHL who are pregnant requires special considerations because of the poor prognosis without treatment. Treatment during the first trimester is associated with significant risk to the developing fetus and should be avoided. Treatment during the second or third trimester should include standard chemotherapy despite the potential risk to the developing fetus.¹⁵³

PROGNOSIS. Good prognostic features include age under 60 years, limited disease at diagnosis (stage I or II), lack of extranodal disease, and a normal lactate dehydrogenase (LDH) level. Individuals with NHL survive for long periods when involvement is only regional. The presence of diffuse disease reduces survival time.

The indolent lymphomas are usually systemic and widespread and cure cannot be achieved, whereas intermediate- and fast-growing lymphomas are more likely to present as treatable and even curable localized disorders but require aggressive therapy.

The prognosis for people with high-grade lymphomas depends on their response to treatment. More specifi-

cally, DLBCL can be cured in 40% to 50% of clients with therapy, follicular lymphoma has a 5-year survival of 60% to 70% (although it is eventually fatal), 20% of clients with mantle cell are alive at 5 years, and Burkitt's lymphoma has a 50% 5-year survival with intensive therapy. In general, the 5-year survival rate for NHL is 63% and the 10-year survival rate is 49%.

Traditionally high-grade NHL associated with AIDS was associated with an extremely poor prognosis. But since the advent of antiretroviral therapy for HIV and a multidisciplinary approach to complex AIDS cases involving malignancy, return to functional health has become possible for many individuals; survival rates approach those seen in persons without HIV.^{48,111,112}

Prognostic indicators for decreased survival in HIV NHL include age greater than 35 years, history of injection drug use, CD4 cell count less than 100/100 ml, a history of AIDS before the diagnosis of lymphoma, stage III or IV disease, and/or elevated LDH levels.¹¹⁰

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-8

Non-Hodgkin's Lymphoma

See Special Implications for the Therapist: Hodgkin's Disease in this chapter.

PREFERRED PRACTICE PATTERNS

See *Hodgkin's disease; neuromuscular patterns may be appropriate in NHL for lymphoma of the nervous system.*

Although uncommon, the association between the use of methotrexate in RA and the development of lymphoma has been reported.^{23,42} Anytime an individual receiving methotrexate for RA complains of back pain accompanied by constitutional symptoms and/or GI symptoms and/or the therapist palpates enlarged lymph nodes at any of the nodal sites, a medical referral is warranted.

Multiple Myeloma

Definition and Overview. Multiple myeloma (MM) is a primary malignant neoplasm of plasma cells arising in the bone marrow. This tumor initially affects the bones and bone marrow of the vertebrae, ribs, skull, pelvis, and femur. Progression of the disease causes damage to the kidney, leads to recurrent infections, and often affects the nervous system. The extent, clinical course, complications, and sensitivity to treatment vary widely among affected people.

Incidence and Etiologic Factors. The incidence of MM has doubled in the past 2 decades, with an annual incidence of approximately 16,570 cases in the United States and 11,310 deaths from MM in the United States in 2006.^{10,91} Since more people are living longer, much of this increase is due to the occurrence of MM in people over the age of 85 years.

MM occurs less often than the most common cancers (e.g., breast, lung, or colon), but its incidence is double that of HL. This disease can develop at any age but is most commonly seen in older people. The median age of diag-

nosis is 69 years for men and 71 years for women; only 5% of clients with MM are younger than 40 years.

Black men are affected twice as often as white men,^{13,8} and MM is slightly more common in men than in women. Risk factors and the cause of MM are unknown, but exposure to ionizing radiation may be linked. Certain occupational hazards found in the petroleum, leather, lumber, and agricultural industries may be linked as well.

Pathogenesis. MM is a malignancy that increases the rate of cell division of plasma cells produced in bone marrow. In the normal development of plasma cells, a hematopoietic stem cell in the bone marrow gives rise to an immature B lymphocyte. This cell then enters the bloodstream and travels to lymphoid tissue. Here it is activated by an antigen-presenting cell and exposed to an antigen, becoming a centroblast.

Centroblasts undergo a maturation process that requires gene rearrangements and switching its Ig isotype from IgM to IgG or IgA. Centroblasts become centrocytes, which then differentiate into plasmablasts or memory B cells. Plasmablasts then migrate back to the bone marrow and terminally differentiate into plasma cells, which no longer divide.

Although it is unknown which cell is the progenitor to the malignant clonal plasma cells, research suggests that it involves the memory B cell or plasmablast—cells that have already been exposed to antigen and undergone gene rearrangements. It is during these times of rearrangement in the gene's coding for the immunoglobulin that breaks naturally occur and mutations can occur, leading to MM.

While this process takes place in lymph tissue (where MM is not typically involved), these cells leave and acquire adhesion molecules, allowing them to attach to the bone marrow stromal cells (structure cells of the bone marrow). It is also these adhesion molecules that attract malignant plasma cells together, forming plasmacytomas or masses of plasma cells.

Similar to other cancers, these clonal cells require the aid of surrounding cells for survival and proliferation. Stromal cells, once a myeloma cell attaches, release cytokines and inflammatory proteins such as IL-6 and IL-1, and tumor necrosis factor (TNF). These proteins then induce the stromal cells to express a surface protein that binds osteoclast precursor cells, inducing them to mature and differentiate. Osteoclasts then break down bone.

This process can be inhibited by osteoprotegerin (OPG), which is secreted by many cell types, but myeloma cells are able to internalize and break down OPG. This leads to an imbalanced situation in the bones, with increased osteoclast activity and reduced OPG. What is unknown is why osteoblasts (bone building cells) undergo apoptosis (programmed cell death). These areas of bone destruction can be seen on plain radiographs, CT, or MRI.

These clonal plasma cells also release high concentrations of immunoglobulins known as M-protein. Monoclonal immunoglobulins in the urine are termed Bence Jones protein. These proteins contribute to renal dysfunction and suppress normal immunoglobulin synthesis.

This decreased level of normal antibodies leaves people with MM unable to adequately respond to infections.

Bleeding problems are seen in 15% to 30% of clients with MM. Although thrombocytopenia is uncommon in the early stages of the disease (IL-6 may stimulate megakaryocytes), acquired coagulopathies or platelet dysfunction can occur. Anemia is common due to low levels of erythropoietin and increased levels of cytokines that decrease the production of erythrocytes.

Clinical Manifestations. The onset of MM is usually gradual and insidious. Common presenting features include fatigue, bone pain, and recurrent infections. Fatigue is a frequent problem due to anemia and elevated levels of cytokines.

Infections are common, particularly gram-negative organisms (60% of infections). MM in older adults (older than 75 years) is the same as that reported in younger people except for a higher rate of infection in the older population.¹⁶¹ These malignant plasma cells can also form large masses known as plasmacytomas, which can grow in bones and soft tissues.

Musculoskeletal. Most people with MM develop bone pain (more than two thirds present with it) and other bone-related problems as bone marrow expands and bone is destroyed. The initial symptom is usually bone pain, particularly at the sites containing red marrow (ribs, pelvis, spine, clavicles, skull, and humeri). Bone loss, the major clinical manifestation of MM, often leads to pathologic fractures, spinal cord compression, osteolysis-induced hypercalcemia, and bone pain.

Initially the bone pain may be mild and intermittent or may develop suddenly as a severe pain in the back, rib, leg, or arm, which is often the result of an abrupt movement or effort that has caused a spontaneous (pathologic) bone fracture. The pain is often radicular and sharp to one or both sides and is aggravated by movement. Symptoms associated with bone pain usually subside within days to weeks after initiation of systemic chemotherapy, but if the disease progresses more areas of bone destruction develop.

Bone destruction leads to hypercalcemia, seen in 30% to 40% of people with MM, which can be life threatening. Symptoms of hypercalcemia may include confusion, increased urination, loss of appetite, abdominal pain, constipation, and vomiting (see the section on hypercalcemia in Chapter 5).

Muscular weakness and wasting affect nearly half of all individuals with cancer and contribute to the cause of cancer-related fatigue. Muscle wasting occurs as a result of disuse, pathology, anemia, nutritional imbalances, or decreased rates of muscle protein synthesis.⁶

Renal. Renal impairment is a common complication of MM, occurring in 50% of all cases at some stage in the disease process. The pathogenesis is multifactorial, but myeloma of the kidney and hypercalcemia account for two of the major causes.

The large amount of monoclonal light chains secreted by the malignant plasma cells can form large casts in the tubules of the kidneys, causing dilation and atrophy, which leads to the inability of the nephron to function and interstitial nephritis. Hypercalcemia occurs from increased bone destruction and absorption of calcium into the blood. In an effort to rid the body of the excess calcium, the kidneys increase the output of urine, which

can lead to serious dehydration and result in further kidney damage if intake of fluids is inadequate.

Calcium can also be deposited in the kidney, creating another source of interstitial nephritis. Hypercalcemia is a common presenting feature but is less common after adequate chemotherapy. Recurrent urinary tract infections are also common and detrimental to the kidneys.

Many medications are nephrotoxic, including some antibiotics, radiographic dyes, and chemotherapy agents. NSAIDs can reduce blood flow to the kidneys, causing further damage. Because of the many factors that can cause injury to the kidneys, nephrotoxic medications should be avoided or used with caution in clients with MM since renal dysfunction and renal failure can occur.

Neurologic. Neurologic complications of MM stem from bone loss or tumor invasion or are protein related. As bone is destroyed in the vertebrae, collapse of the bone with subsequent compression of the nerves can occur. Clients may complain of back pain, numbness, tingling, or loss of strength.

Large plasmacytomas (particularly in the spinal canal or skull) can compress nerves, leading to spinal cord or cranial nerve compressions. Spinal cord compression is usually observed early or in the late relapse phase of the disease. Presenting symptoms include back pain with radiating numbness/tingling, muscle weakness or paralysis of the lower extremities, and loss of bowel or bladder control.

Spinal cord compression is a medical emergency requiring immediate attention. High concentrations of protein are also neuropathic. Amyloidosis (deposits of insoluble fragments of a protein) develops in approximately 10% of people with MM (up to 35% have asymptomatic amyloidosis). These deposits cause tissues to become waxy and immobile and may affect nerves, muscles, and ligaments, especially the carpal tunnel area of the wrist. Carpal tunnel syndrome with pain, numbness, or tingling of the hands and fingers may develop. The association between MM and RA, Sjogren's syndrome, and other autoimmune diseases has been established, but it is not clear why this occurs.

MEDICAL MANAGEMENT

DIAGNOSIS. The diagnosis of MM is determined by clinical factors as well as bone marrow examination. Because other diseases also present with an elevated monoclonal gammopathy, new criteria have been developed by the International Myeloma Working Group to aid in the diagnosis and distinction of these paraprotein diseases in order to provide appropriate treatment.³⁹

Major and minor criteria were created to distinguish MM from asymptomatic myeloma and monoclonal gammopathies of undetermined significance (MGUS). Clients must have at least one major and one minor or three minor criteria to be diagnosed with MM (Table 14-5). Major features consist of an elevated M-protein level or Bence Jones proteinuria, plasmacytoma on a tissue biopsy, and greater than 30% of clonal plasma cells on bone marrow biopsy examination. Individuals who demonstrate increased levels of M-protein but do not exhibit end-organ damage have asymptomatic (smoldering) myeloma.

Table 14-5 Criteria for the Diagnosis of MM

Major Criteria	Minor Criteria
Plasmacytoma by biopsy of tissue	Bone marrow shows clonal plasma cells 10%-30%
Bone marrow shows clonal plasma cells >30%	M-protein less than that for major criteria (IgG < 3.5 g/dl, IgA < 2.0 g/dl)
High M-protein (IgG > 3.5 g/dl, IgA > 2.0 g/dl)	Lytic bone lesions on radiograph or MRI
Bence Jones proteinuria >1.0 g/24 hr	Reduced levels of nonmonoclonal immunoglobulins (IgM < 50 mg/dl, IgA < 100 mg/dl, or IgG < 600 mg/dl)

Modified from Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group, *Br J Haematol* 121:749-757, 2003.

Clients who express low amounts of protein, have less than 10% of plasma cells in the bone marrow, and have no end-organ damage are diagnosed with MGUS. Approximately 12% of clients with MGUS will develop MM, macroglobulinemia, other lymphoproliferative disease, or amyloidosis within 10 years; this risk increases to 25% at 20 years (i.e., a minority of people with MGUS will develop MM).¹⁰⁵ The factor that correlates best with the progression of MGUS to MM is the concentration of M-protein at diagnosis.

Tests performed to determine if criteria are met for the diagnosis of MM include a bone marrow biopsy, measurement of M-protein in the blood and urine (serum protein electrophoresis and urine protein electrophoresis, respectively, or more sensitive tests such as Immunoelectrophoresis and immunofixation), biopsy of any suspect mass, and radiographic skeletal survey (lytic lesions also seen on CT and MRI).

Other tests that are helpful in providing prognostic information include LDH, β_2 microglobulin, plasma cell labeling index (a measurement of the proliferative capacity of the myeloma cells), and cytogenetics (to determine specific mutations and abnormalities). Both plasma cell labeling index and cytogenetic tests are obtained by bone marrow aspiration. PET scans can also reveal probable areas of tumor involvement, while β_2 microglobulin, a small protein, reflects tumor load.

Evaluation of symptoms may include an assessment of serum calcium, kidney function, CBC, quantitative immunoglobulins, and cultures (for any suspected infections).

TREATMENT. The center of treatment of MM includes the elimination of malignant plasma cells and correction of problems in the bones and other organs. For decades, standard treatment for MM has been intermittent cycles of melphalan plus prednisone or a combination of alkylating agents when progression of disease occurs. Survival with these agents alone is approximately 3 years.

The introduction of high-dose (myeloablative) chemotherapy using melphalan with stem cell support in the initial treatment of MM significantly improved the outcomes, with increased complete remission rate and extended disease-free and overall survival. Later research found that two high-dose courses of melphalan, each followed by an infusion of autologous stem cells, was superior to a single treatment, particularly for clients who did not respond to the first transplant.¹⁴

This double transplant is best for people whose myeloma cells have a normal karyotype. In these clients

remission at 10 years was nearly 20%. Efforts are being made to find ways to overcome drug resistance and reduce the ability of environmental cells to aid in the survival and proliferation of myeloma cells.

Three drugs available are thalidomide, lenalidomide, and bortezomib. All three agents have shown superiority to conventional drugs in refractory and relapsed disease, and studies are ongoing to determine their use in earlier treatment. Thalidomide, an infamous oral agent, has shown significant improvement in response rates as a preparatory agent for autologous BMT compared with conventional agents.

When used in maintenance therapy following transplant, thalidomide improved event-free survival compared with no maintenance therapy. Yet thalidomide has not been shown to improve overall survival when used before and after double transplants.¹⁶ Because thalidomide does cause significant fetal malformations, increased thromboembolic risks, and severe neuropathy, an analogue (lenalidomide) was designed in hopes of reduced side effects. While lenalidomide lacks the adverse effect of severe neuropathy, it does cause neutropenia.

Another newly introduced medication is bortezomib, a proteasome inhibitor (a proteasome degrades other proteins, keeping a balance of proteins in a cell). It is currently approved for refractory and relapsed myeloma.¹⁵⁷ Further research is needed to determine which drugs are most effective and when. Oncologists are looking toward individualizing treatment depending on the types of mutations present in the myeloma cells.

Advances have also been made in correcting symptoms caused by the myeloma and surrounding cells. Bone pain is one of the most significant problems faced by clients with MM. Pathologic fractures are treated with surgery and pain control. Lytic lesions often require radiation for pain relief along with opiates. Radiation may be all that is needed to decrease pain and stabilize the cervical spine when metastases occur. In some cases radiation has been shown to stop and even reverse bone destruction.^{66a}

Monthly infusions of the bisphosphonates pamidronate and zoledronic acid have been shown to be effective when used with chemotherapy, not only in the improvement of bone lesions but also in decreasing the need for radiation, decreasing osteoporotic fractures, and improving survival in some people with myeloma (median survival is 1 year compared with 3 or 4 months with BMT).^{20,185}

Bisphosphonates are potent inhibitors of osteoclastic activity (resorption) and may exert an antitumor effect

that is apoptotic and antiproliferative.⁵² Hypercalcemia is treated with hydration, corticosteroids, and bisphosphonates. Anemia improves with myeloma treatment, but the use of erythropoietin can speed up recovery of erythrocyte production.

Future treatment under investigation includes peripheral stem cell grafting, posttransplant immunotherapy, gene therapy, new drugs, development of effective oral bisphosphonates, new ways of delivering radiotherapy to specific sites, and radiopharmaceuticals that concentrate at involved marrow sites.²⁰³ A tumor-specific vaccine for active immunization is also under investigation.⁷⁴

PROGNOSIS. Despite 30 years of clinical trial research conducted by three major cooperative groups under the auspices of the National Cancer Institute, the prognosis for MM has not markedly improved and it remains an incurable disease. With standard therapy, the median survival of clients with MM remains about 3 years.

The advent of double transplants has improved the median survival, with the estimated overall 7-year survival rate of 21% for people receiving a single transplant and 42% for those receiving a double transplant (two high-dose courses).¹⁴ Yet individual responses are varied and a client's prognosis cannot be accurately predicted. As in lymphomas and leukemias, scientists are looking for genetic factors that will not only aid in directing therapy, but prognosis as well.²⁰⁷

Some of the risk factors for a poor prognosis include a high serum C-reactive protein (a surrogate marker for IF-6 activity), β_2 microglobulin, or LDH (both reflecting tumor load). Other poor risk factors are an elevated plasma cell labeling index, detection of circulating plasma cells, and involvement of the CNS by myeloma cells (malignant cells in the CSF accompanied by signs and symptoms of CNS involvement).

Some of the cytogenetic prognostic factors include deletion of chromosomes 13 and 17 and alterations in chromosome 1. The development of bisphosphonates, thalidomide, and bortezomib has aided in changing the local myeloma environment and in reducing resistance of tumor cells to commonly employed cytotoxic drugs.

If untreated, unstable MM can result in skeletal deformities, particularly of the ribs, sternum, and spine. Diffuse osteoporosis develops, accompanied by a negative calcium balance. Prognosis is affected by the presence of renal failure (poorer prognosis if present at the time of diagnosis), hypercalcemia, or extensive bony disease; infection and renal failure are the most common causes of death.

Future improvements with transplantation may be achieved by providing tumor-free grafts and posttransplant treatment aimed at eradicating minimal residual disease.

SPECIAL IMPLICATIONS FOR THE THERAPIST

14-9

Multiple Myeloma

PREFERRED PRACTICE PATTERNS

4A: Primary Prevention/Risk Reduction for Skeletal Demineralization (bone loss and osteoporosis)

4B: Impaired Posture (skeletal deformity; bone pain)

4D: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Connective Tissue Dysfunction (for those with arthritic component)

4G: Impaired Joint Mobility, Muscle Performance, and Range of Motion Associated with Fracture

5G: Impaired Motor Function and Sensory Integrity Associated with Acute or Chronic Polyneuropathies (carpal tunnel syndrome associated with local dissemination of neoplasm)

5H: Impaired Motor Function, Peripheral Nerve Integrity, and Sensory Integrity Associated with Nonprogressive Disorders of the Spinal Cord

MM can have severe and devastating effects on the musculoskeletal system. Fatigue and skeletal muscle wasting can result in a weak and debilitated individual who is at risk for falls and subsequent musculoskeletal injuries. Bone pathology with fracture can also be very painful and disabling, affecting function and quality of life. The therapist may be instrumental in early detection and referral to minimize detrimental secondary effects.⁹⁴

Multiple Myeloma and Exercise

Therapists can assist individuals with MM to manage both the disease and treatment-related symptoms, improve overall quality of life, and prevent further complications associated with decreased activity and exercise.

The therapist may play an important role in various stages of the progression of this disease, including prevention and management of skeletal muscle wasting, cancer-related fatigue, and pathologic fractures.⁹⁴ Individualized exercise programs for individuals receiving aggressive treatment for MM may be effective for decreasing fatigue and mood disturbance and for improving sleep.³⁷

Symptoms such as fatigue can be so overwhelming at times that some people have even said that they would rather just die than continue suffering the extremes of fatigue and malaise.⁴⁰ The National Comprehensive Cancer Network continues to recommend exercise in their updated clinical practice guidelines for the management of cancer-related fatigue.^{128,129}

The guidelines suggest referral to physical therapy for fitness assessment and exercise recommendations with emphasis on getting clients to gradually increase their activity level to avoid sustaining an injury or becoming discouraged. Short, low-intensity exercise programs may be helpful at first. The key is to get the individual to implement and maintain the program.

Individuals with MM have a number of intrinsic and extrinsic factors that can challenge their ability to engage in an exercise program. Intrinsic factors include a belief that exercise will help, a commitment to one's health, creation of personal goals, and a plan to reach them. Extrinsic factors include a good support system and adequate medical care (e.g., prophylactic epoetin alfa used to treat anemia).³⁸

The therapist's ability to implement falls assessment and prevention programs can be a life-saving intervention for the individual at risk for pathologic fractures. Exercise interventions to improve function and decrease muscle wasting and cancer-related fatigue during and after cancer treatment for MM have been shown effective. Suggested exercise protocols for MM are available.¹⁸²

Complications

Specific examination and evaluation can provide early recognition of complications such as hypercalcemia and spinal cord compression. Any symptoms of hypercalcemia (see Clinical Manifestations in this section) must be reported to the physician; the client should seek immediate medical care since this condition can be life threatening. (For the client with amyloidosis, anemia, or renal failure, see the Special Implications for the Therapist for each of these conditions.) Adequate hydration and mobility help minimize the development of hypercalcemia.

The client with MM who develops signs of cord compression must be referred to the physician. Emergency MRI is required to locate the area of cord compression. A laminectomy may be required when spinal cord compression occurs, but immediate radiation and high-dose glucocorticoid therapy usually relieve the compression, avoiding the need for surgical intervention.

Spinal instability may be a problem. Orthopedic back braces may help with pain management and reduce the risk of further trauma but are often poorly tolerated; newer lightweight supports with hook-and-loop fasteners may be more useful. Vertebroplasty and kyphoplasty procedures may help improve spinal stability; cement injected into the collapsed vertebrae reinforces the bone. In the case of kyphoplasty, vertebral height is restored.⁵⁵

Weight Bearing

There is little clinical evidence to guide the therapist in choosing a safe amount of weight bearing through cancer-lysed metastatic bone during exercise, transfers, ambulation, or other activities of daily living skills.⁹⁴ Some general guidelines based on radiographic findings have been suggested for individuals with bone metastases⁹⁵:

>50% (cortical metastatic involvement)	Non-weight bearing with crutches or walking; touch down permitted
25% to 50%	Partial weight bearing; avoid twisting or stretching
0% to 25%	Full weight bearing; avoid lifting or straining

These recommendations must be used with caution, taking into consideration the client's age, general health, overall level of fitness, and level of pain. Through careful assessment, the therapist guides the client in maintaining mobility as much as possible

while preventing fracture. Continual monitoring of symptoms to detect developing or new fracture is imperative. The affected individual must be taught what to look for and when to seek medical attention if signs and symptoms of new fracture appear.

Supportive and Palliative Care

In preterminal and terminal stages, attention to supportive therapy and palliation are integral and can make a great impact on the individual and family's quality of life. The role of the therapist increases in late stages when immobility and renal failure complicate the clinical picture.¹⁵⁵

Myeloproliferative Disorders

Myeloproliferative disorders are a group of diseases that originate from a hematopoietic stem cell that has undergone a transformation. This transformation allows the cells to mature and function, yet there is uncontrolled production. Myeloproliferative disorders also share other characteristics, including a hypercellular bone marrow, tendency toward thrombosis and hemorrhage, and an increased risk of evolving into acute leukemia over time.²⁸

The four main myeloproliferative diseases are CML, polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis. While all of these disorders can exhibit elevations in all cell lines, each disease has a main cell line that is affected.

Polycythemia vera is an uncontrolled production of erythrocytes. Essential thrombocythemia is characterized by an elevated platelet count. Excessive fibrosis of the marrow is a dominant feature of idiopathic myelofibrosis. Myelofibrosis and other more rare diseases are not covered in this text. CML is discussed with the leukemias.

Polycythemia Vera

Definition, Overview, and Etiologic Factors. Polycythemia (rubra) vera (PV) is a myeloproliferative disorder of bone marrow stem cells affecting the production of erythrocytes. The diagnosis of polycythemia means an elevated RBC mass that may be primary or secondary.

Secondary polycythemia is typically acquired as a result of decreased oxygen availability to the tissues; the body attempts to compensate for the reduced oxygen by producing more erythrocytes (e.g., smoking, high altitudes, and chronic heart and lung disorders). However, PV is a primary cause of polycythemia and results from a genetic abnormality that allows erythrocytes to mature and function, but in an uncontrolled fashion.

The incidence of PV is approximately two to three cases per 100,000.¹⁵² PV develops following a transformation of a hematopoietic stem cell. The etiologic factors of PV are attributed to benzene and other occupational exposures, including radiation. It typically occurs in older people between age 50 and 60 years (people with PV younger than 30 years is rare), with a slightly higher incidence in men than in women.

Pathogenesis. Recently specific mutations have been discovered that tie many of the myeloproliferative disorders together. One, reported in 2005, was a change in Janus kinase 2 (JAK2). This protein normally initiates intracellular signals after a cell membrane receptor binds erythropoietin, thrombopoietin, IL-3, GCSF, or granulocyte-macrophage CSF.²⁸

Once JAK2 is activated, a cascade of signals is sent that leads to the production of cells. In up to 95% of clients with PV, there is a mutation in the *JAK2* gene. Valine is replaced for phenylalanine at position 617 (V617F). This region normally exerts a negative effect in that it controls signals and the production of cells. But with this mutation cellular production occurs despite the lack of binding cytokines (cells become cytokine independent), leading to many of the problems seen in myeloproliferative disorders, including PV.

Other genetic abnormalities are also described, and several genetic modifications are most likely required for cellular transformation. There is also an increased risk of PV evolving into AML over time. Although the mechanisms are not understood, clients without the *JAK2* mutation can develop AML, demonstrating that other mutations may be the source.

Clinical Manifestations. Symptoms are related to hyperviscosity, hypervolemia, and hypermetabolism. The increased concentration of erythrocytes may cause hypertension or neurologic symptoms such as headache, blurred vision, feeling of fullness in the head, disturbances of sensation in the hands and feet, and vertigo.

Blockage of the capillaries supplying the digits of either the hands or feet may cause a peripheral vascular neuropathy with decreased sensation, burning numbness, or tingling. This same small blood vessel occlusion can also contribute to the development of cyanosis and clubbing of the digits. If untreated, the worst case scenario may include gangrene, requiring amputation.

The client may demonstrate increased skin coloration (e.g., ruddy complexion of face, hands, feet, ears, and mucous membranes), and splenomegaly is common. Dyspnea may develop secondary to hypervolemia. Abnormal interactions among erythrocytes, leukocytes, platelets, and the endothelium lead to thrombosis (e.g., splenic infarctions and Budd-Chiari syndrome, which is a thrombosis of the hepatic vein) or bleeding (e.g., easy bruising, GI bleeding, and epistaxis).

Gout and uric acid stones may develop because of hypermetabolism. Intolerable pruritus (itching), especially after bathing in warm water, may be prominent. The symptoms of PV are often insidious in onset and characterized by vague complaints such as irritability, general malaise and fatigue, backache, and weight loss. Diagnosis may not be made until a secondary complication, such as stroke or thrombosis, occurs.

MEDICAL MANAGEMENT

DIAGNOSIS. Diagnosis is established by history, examination, and laboratory analysis. The erythrocyte count is greater than 60% of normal for men and 56% for women (without the presence of secondary polycythemic factors). WBC and platelet count are often elevated in people

with PV and are normal in most people with secondary polycythemia.

The presence of the *JAK2* mutation can be identified by PCR and other sensitive tests. A positive *JAK2* and appropriate clinical factors may be enough information to make the diagnosis. However, since not all cases of PV express the *JAK2* abnormality, other tests can be performed.

These include labeling RBCs with chromium to distinguish between absolute polycythemia (increased RBC mass) and relative polycythemia (normal RBC mass but decreased plasma volume), growing cells to verify erythropoietin independence, measuring plasma erythropoietin, evaluating cytogenetic studies of the bone marrow, and performing an ultrasound of the spleen to demonstrate splenomegaly.

TREATMENT. Treatment goals are to reduce erythrocytosis and blood volume, control symptoms, and prevent thrombosis. Repeated phlebotomy is used to maintain stable Hb (less than 45%) by causing iron deficiency.

Clients who are older than 70 years, have a history of thromboembolism, or have a platelet count greater than 400,000/ μ l are treated with the antimetabolite hydroxyurea, which does not appear to be associated with an increased incidence of acute leukemia (alkylating agents are linked to leukemia).

Aspirin, if no contraindications exist, has been found to be beneficial to all people with PV in reducing the risk of thrombotic events, although overall mortality and cardiovascular mortality rates are not significantly reduced.¹⁰⁷

PROGNOSIS. The prognosis for PV is good, and median survival is 15 years with appropriate treatment. Without proper treatment, the mortality rate (18 months from the time of symptomatic onset) is 50%. The risk for stroke, myocardial infarction, and thromboembolism is high for people with this condition; thrombosis or hemorrhage is the major cause of death. Late in the course of this disease bone marrow may be replaced with fibrous tissue (myelofibrosis) or transform into AML.

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-10

Polycythemia Vera

PREFERRED PRACTICE PATTERNS

4E: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Localized Inflammation (gout)

6A: Primary Prevention/Risk Reduction for Cardiovascular/Pulmonary Disorders (myocardial infarction and stroke prevention; thromboembolism)

Thrombosis occurs more often in clients with PV, which requires the therapist to be alert to any possible signs of Budd-Chiari syndrome (abdominal pain, ascites, and liver function abnormalities) and deep vein thrombosis or stroke (e.g., weakness, numbness, inability to speak, visual changes, headache; see the section on thrombophlebitis in Chapter 12).

GI bleeding, bruising, and epistaxis are also common. Watch for other complications such as dyspnea and splenomegaly. If the person has symptomatic splenomegaly, follow precautions for soft tissue techniques required in the left upper quadrant, especially up and under the rib cage. These procedures must be secondary or indirect techniques away from the spleen.

Essential Thrombocythemia

Overview and Etiology. Essential thrombocythemia (ET) is one of the most common myeloproliferative disorders. It is defined as a disease with a platelet count greater than 600,000/ μ l without secondary causes for an elevated number of platelets.

ET is a primary thrombocytosis disorder resulting from a transformation of a hematopoietic stem cell and occurs most frequently in middle-aged to older adults (average age of onset between 50 and 60 years). There may be more of a predisposition for women to develop the disease than men.

Secondary causes of thrombocytosis occur as a result of conditions such as acute bleeding, iron deficiency, infection (e.g., tuberculosis), chronic inflammatory disease (e.g., RA), and malignancy and resolve with treatment of the underlying pathology.¹⁶⁶ Secondary thrombocytosis may also be seen following splenectomy because platelets that normally would be stored in the spleen return to the circulating blood.

Pathogenesis. About 50% of clients with ET demonstrate the JAK2 mutation (a mutation that leads to uncontrolled cell proliferation), linking it with other myeloproliferative disorders (see above section on PV). Persons who carry the JAK2 V617F mutation may be at higher risk for thrombotic complications than other ET clients without this mutation.¹⁶⁷ Thrombosis may develop as a result of an abnormal interaction among leukocytes, platelets, and endothelium.¹⁶⁸ Other genetic abnormalities are most likely responsible for the remaining cases that do not exhibit JAK2.

Clinical Manifestations. The most prominent feature is a platelet count elevation above 600,000/ μ l. Most people with ET also exhibit splenomegaly (50%) and episodes of bleeding and/or thrombosis. Up to one third of clients are diagnosed from a routine blood count while asymptomatic.

Visual disturbances, headache, burning sensation of the feet and hands accompanied by redness (secondary to vasodilatation; erythromelalgia), and skin changes (livedo reticularis; Fig. 14-10) develop with increasing platelet counts. The most serious complications, bleeding and thrombosis, occur secondary to platelet dysfunction. Although major bleeding is uncommon, the likelihood increases as platelet counts exceed 1,500,000/ μ l. Thrombotic complications occur in up to 30% of people with ET.

MEDICAL MANAGEMENT

DIAGNOSIS. The differentiation between reactive thrombocytosis (i.e., secondary thrombocytosis) and ET can be



Figure 14-10

Livedo reticularis associated with thrombocythemia (elevated platelet count). The classic fishnet pattern is shown. (Reprinted from Piccini JP, Nilsson KR: *The Osler medical handbook*, ed 2 2006, the Johns Hopkins University.)

difficult. The presence of the JAK2 mutation (by PCR), splenomegaly, and abnormal bone marrow is indicative of ET since other causes of thrombocytosis do not include these features. For a high percentage of cases other tests must be performed.

TREATMENT. The treatment of ET depends on the age and symptoms of the person. Asymptomatic, young clients (age less than 60 years) with a platelet count less than 1,500,000/ μ l may not require treatment. Hydroxyurea is used for people who are older than 60 years with a history of a thrombotic event to reduce the platelet count to less than 400,000/ μ l. This therapy significantly reduces the risk of another thrombotic event.

Anagrelide is another medication used to reduce the platelet count; however, it has been linked to a higher risk of arterial thrombosis, bleeding, and transformation of the bone marrow to myelofibrosis compared with hydroxyurea.¹⁶⁹

Aspirin may be of benefit for clients who are at high risk for thrombosis and do not have a history of bleeding. Persons who develop acute ischemic events and have a platelet count greater than 1,500,000/ μ l should receive immediate plateletpheresis. If surgery is required, the platelet count should be brought to near normal levels to reduce the risk of bleeding and thrombosis perioperatively.

PROGNOSIS. Most people with ET have near normal life expectancies. ET carries a small (3% to 4%) risk of transforming into acute leukemia and rarely develops into myelofibrosis. Bleeding and thrombotic events are the most serious complications and can be life threatening. Better understanding of the mutations resulting in ET may lead to improved treatment and prophylaxis against bleeding and thrombotic complications.

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-11

Thrombocythemia

The therapist may recognize this condition when the client presents with livedo reticularis accompanied by reports of headache, burning sensation in the hands and feet, and visual disturbances. Medical referral is required if the person has not been previously evaluated.

In cases of known thrombocythemia, the therapist must maintain surveillance for arterial and venous thrombotic episodes and educate the client about what to watch for and when to seek medical assistance immediately. Signs and symptoms of arterial emboli include pain, numbness, coldness, tingling or changes in sensation, skin changes (pallor, mottling), weakness, and muscle spasm occurring in the extremity distal to the block (see Table 12-19).

With venous occlusion, the tissues are oxygenated but the blood is not moving and stasis occurs. The skin is discolored rather than pale (ranging from angry red to deep blue-purple), edema is present, and pain is most marked at the site of occlusion, although extreme edema can render all the skin of the limb quite tender.

DISORDERS OF HEMOSTASIS

Hemostasis is the arrest of bleeding after blood vessel injury and involves the interaction among the blood vessel wall, the platelets, and the plasma coagulation proteins. Normal hemostasis is divided into two separate and independent processes: primary and secondary.

Primary hemostasis involves the formation of a platelet plug at the site of vascular injury. When a vessel is disrupted, collagen fibrils and von Willebrand's factor (vWF) in the subendothelial matrix of the blood vessel become exposed to blood. The vWF (which is usually coiled when inactive) in the plasma and the subendothelium becomes uncoiled and binds the collagen fibrils to the platelets via special receptors on the platelets. This ultimately leads to the formation of a platelet plug.

Secondary hemostasis is triggered when vascular damage exposes tissue factor. Tissue factor is found in places not normally exposed to blood flow, where the presence of blood is pathologic. It is present in significant amounts in the brain, subendothelium, smooth muscle, and epithelium. Tissue factor is not found in skeletal muscle or synovium, the usual locations for spontaneous bleeding in people with hemophilia.

Tissue factor then binds the clotting factor VII, which in turn activates factor X and IX. This eventually leads to the formation of thrombin, which cleaves fibrinogen into fibrin, creating a fibrin clot at the site of injury.

Normal primary hemostasis requires normal number and function of platelets and vWF. Persons who have abnormalities in primary hemostasis have defects in either the number or function of platelets or a deficiency or dysfunction of vWF.

A decrease in the number of platelets, called *thrombocytopenia*, can prevent hemostasis. An exceptionally high number of platelets, called thrombocytosis, may cause bleeding, thrombosis, or both (see section on ET). Persons with a deficiency or dysfunction in vWF have von Willebrand's disease (vWD).

Bleeding caused by platelet disorders or vWD is characterized by mucosal or skin bleeding. Normal secondary hemostasis necessitates the presence of clotting factors. Defects in secondary hemostasis result from clotting factor deficiencies or dysfunction, such as those seen in hemophilia A and B. Persons with abnormalities in secondary hemostasis tend to have more serious bleeding such as deep muscle hematomas and spontaneous hemarthrosis.

von Willebrand's Disease

Definition and Overview

von Willebrand's disease (vWD) is the most common inherited bleeding disorder and is caused by a lack of or dysfunction of vWF. The prevalence of this illness may be as high as 1% to 2% of the population (based on population screening studies), yet studies that used only data from clients referred for bleeding disorders found only 30 to 100 cases per 1 million, which is similar to hemophilia A.¹⁶⁰

vWF is a large molecule made of multiple glycoproteins (dimers). It is produced by megakaryocytes, which secrete vWF into the blood plasma, and also by vascular endothelial cells, which release it into the subendothelial matrix. The function of vWF is to bind collagen fibrils and platelets in areas of vascular injury to create a platelet plug. It also stabilizes factor VIII and prevents it from being inactivated and cleared from the plasma during times of bleeding.

vWD is classified into three main subtypes: types 1, 2, and 3. Type 1 is the most common subtype and accounts for 60% to 80% of clients with vWD. Persons with this subtype have 5% to 30% of the normal amount of vWF, leading to mild to moderate symptoms. Type 1 is inherited through an autosomal dominant fashion.

Type 2 is less common and seen in only 10% to 30% of vWD cases. It is caused by a dysfunction in vWF rather than a reduction in quantity of vWF. Because the severity of the abnormality can vary, this subtype is further divided into types 2A, 2B, 2M, and 2N. This subtype is also inherited in an autosomal dominant manner.

The rarest of vWD subtypes is type 3, which makes up only 1% to 5% of cases. Persons affected with this form have less than 1% of the normal plasma levels of vWF (levels may be undetectable) and very low levels of the clotting factor VIII. Because these clients are lacking both vWF and factor VIII, their symptoms are more severe and resemble hemophilia A. Inheritance is autosomal recessive.

Pathogenesis

vWF is produced from a gene located on chromosome 12. Many factors are involved in determining inheritance of the disease, yet often only one mutation on one chromosome leads to minor bleeding problems while

abnormalities on both genes (homozygous) have more serious problems.

vWD occurs due to a qualitative lack of vWF or because of an abnormally functioning vWF (although vWF is produced, a mutation causes a malformation in the function of the proteins). Significant investigation has been placed into the discovery of the genetic abnormalities associated with vWD, and over 250 mutations of multiple types have been documented.⁹⁶

Clinical Manifestations

Symptoms experienced by clients with vWD vary depending on the subtype and severity of the abnormality. Clients with type 1 experience bleeding consistent with a primary hemostasis defect. This most frequently involves mucosal and skin bleeding such as petechiae and prolonged oozing of blood after trauma or surgery.

Other common problems include epistaxis, gum bleeding, and GI bleeding. Symptoms associated with type 2 depend on the severity of the mutation and the quantity of functional vWF. It is estimated that 10% to 20% of women with menorrhagia (excessive menstruation) have vWD. Menorrhagia is a common presenting symptom yet is frequently overlooked and undiagnosed because gynecologists only rarely (less than 1%) perform tests to confirm or exclude a bleeding disorder.^{31,45,53}

Type 3 clients present not only with symptoms of mucosal and skin bleeding but also more frequent and severe symptoms including hemarthrosis and muscular hematomas (similar to hemophilia A).

MEDICAL MANAGEMENT

DIAGNOSIS. The most common screening laboratory tests used to assess coagulation are the activated partial thromboplastin time and the prothrombin time. Despite available tests, many clinicians find making the diagnosis very difficult—particularly for clients with mild disease. Test results are often normal in clients with vWD. vWD cannot be diagnosed with just one laboratory test; the clinician relies on at least four tests to aid in the diagnosis: a platelet function test, vWF antigen test, ristocetin cofactor activity, and factor VIII level.

Two tests help assess platelet function: the bleeding time and a machine called the Platelet Function Analyzer 100 (PFA-100, Dade Behring, Deerfield, IL). The bleeding time test is performed by making small punctures in the skin and then measuring the time until clotting occurs. This test has numerous technical variables and is neither specific nor sensitive for the diagnosis of mild vWD (which may have a normal bleeding time).

The PFA-100 assesses the time required for a small collagen-coated tube to close when exposed to a person's blood. Although this test has fewer technical problems, anemia and other factors may distort the results. Prolonged clotting times can be indicative of a platelet problem, but more specific tests are needed to confirm the diagnosis of vWD.

vWF antigen can be measured in the blood (if vWF is present, the test will be positive). Ristocetin is an antibiotic that binds to vWF and leads to platelet aggregation. Using this information, the quantity of vWF can be approximated by adding plasma from the client to plate-

lets and adding ristocetin. Platelet aggregation will occur at a specific rate depending on the vWF concentration.

Factor VIII levels can be directly measured in the plasma. Subtypes with very low levels of vWF also have low levels of factor VIII (particularly type 3). Collagen binding activity is often measured (since one function of vWF is to bind collagen to platelets) using an enzyme-linked immunosorbent assay type test. Gel electrophoresis can be used to ascertain the subtype of vWD.

Because of the increased frequency of menorrhagia and other bleeding problems related to obstetrics and gynecology, guidelines have been developed that may lead to improved diagnosis and treatment of women with bleeding disorders, particularly vWD.^{2,45}

TREATMENT AND PROGNOSIS. The treatment of vWD centers on the replacement of vWF and/or factor VIII as needed during times of bleeding or prophylactic administration prior to an invasive procedure.¹¹⁸ Most clients with vWD (especially type 1) do not require treatment except during times of surgery or trauma or after delivery of a fetus. Those persons exhibiting more serious complications such as hemarthrosis or frequent GI bleeding (type 3 or some type 2) may require scheduled prophylactic treatment.

Desmopressin is the principal drug of choice for treating most cases of vWD. It is a synthetic antidiuretic-hormone derivative that induces the secretion of vWF and factor VIII from storage. This medication can be given intravenously, subcutaneously, or intranasally.

Since treatment is often needed during emergencies, intravenous dosing is the most practical, although subcutaneous and nasal routes are useful when used for prophylaxis. Vasopressin can increase the levels of vWF and factor VIII three to five times the baseline level within 60 to 90 minutes. It is not effective for type 3 cases (these clients do not make enough to store) and is contraindicated or ineffective for most persons with type 2. Since type 2 vWD results from an abnormal vWF, it is useless to secrete increased amounts of abnormal vWF.

People with types 2 and 3 vWD often require concentrates of factor VIII/vWF for spontaneous bleeding, surgery, or trauma. Humate-P (CSL Behring, King of Prussia, PA), which contains more vWF than factor VIII, and Alphanate (antihemophilic factor), containing equal amounts of vWF and factor VIII, are synthetic concentrates currently available. Both products are virus inactivated through a heat treatment. Wilfactin (LFB, Les Ulis, France), another concentrate, replaces vWF and contains little factor VIII, allowing for the use of the client's own factor VIII (with vWF in the plasma, autologous factor VIII is stable).

If concentrates are not available, other plasma replacements can be used. Fresh frozen plasma contains both vWF and factor VIII but is accompanied by a large volume, and multiple bags can cause volume overload. Cryoprecipitate contains both proteins in a smaller, concentrated volume yet has the potential of being infectious (although rare with current screening).

Other available medications, which are used for dental or minor mucosal bleeding, include antifibrinolytic agents. Along mucosal linings of the body there is

fibrinolytic activity, which prevents fibrin from forming a clot.

Antifibrinolytic amino acids can be given to inhibit this activity. Aminocaproic acid and tranexamic acid are two antifibrinolytic amino acids that can be dosed topically, orally, or intravenously. For clients with minor bleeding problems, these agents may be sufficient for minor procedures. Frequently they are used as adjuvant medications along with concentrates and desmopressin during major and minor surgery.¹¹⁸

Despite advancement in treatment, clients with type 3 vWD still face the challenge of developing inhibitors to available treatment. These inhibitors are typically antibodies that clear vWF from the plasma. Further use of concentrates with vWF can lead to anaphylaxis. Concentrates of factors VIII and VII have been utilized to aid with clot formation with success (and antibodies do not form to pure factor VIII concentrates), although factor VIII has a short half-life without vWF. Research is ongoing to determine strategies for overcoming these issues.

Women with severe symptoms can suppress menstruation with the use of oral contraceptives or receive concentrates when needed for menorrhagia. Studies are pending that may provide better information concerning best treatment options for women with bleeding disorders.

vWF and factor VIII levels do rise with pregnancy, but pregnant clients must be followed very carefully; concentrates and desmopressin are used at birth and during the immediate postpartum period. Care must also be taken when treating the fetus since the baby may have vWD as well. Intramuscular injections, surgery, and circumcision should be avoided in babies with a high risk of a bleeding disorder until an adequate diagnosis is made.^{2,45}

Clients with minor bleeding manifestations have problems that can often be avoided with proper care. Individuals with more serious symptoms and complications have significant alterations in quality of life; surgery and trauma can be life threatening. Currently a vWF concentrate that is produced by recombinant technologies (thereby avoiding all risk for viral infections) is under investigation.¹⁶⁸

Recombinant activated factor VII shows promise as another concentrate that can be used for vWD and for clients with vWD who have developed inhibitors to routine medications and concentrates.⁶⁶ The cytokine interleukin-11 has been noted to increase both factor VIII and vWF levels, and studies are underway to determine efficacy and safety.⁴⁶ Gene therapy is less hopeful since the size of the DNA coding for the many dimers that make up vWF is so large.

Hemophilia

Overview

Hemophilia is a bleeding disorder inherited as a sex-linked autosomal recessive trait. The two primary types of hemophilia are *hemophilia A*, or classic hemophilia, and *hemophilia B*, or Christmas disease. Hemophilia A results from a lack of the clotting factor VIII and constitutes 80% of all cases of hemophilia. Hemophilia B is less common, affecting about 15% of all people with

hemophilia, and is caused by a deficiency of factor IX. Other less-common deficiencies, such as deficiencies of clotting factors I, II, V, VII, X, or XIII, are rare and are not fully discussed in this text. Unless otherwise noted, hemophilia refers to both hemophilia A and B in this text.

Factors VIII and IX are required in secondary hemostasis (in contrast to vWF, which is needed in primary hemostasis). These clotting factors are activated and result in the production of thrombin, which cleaves fibrinogen to fibrin, creating a stable clot.

The level of severity of the disease depends on the defect in the clotting factor gene and is classified according to the percentage of clotting factor present in plasma (determined through blood tests): mild (6% to 30%), moderate (1% to 5%), and severe (less than 1%). Normal concentrations of coagulation factors are between 50% and 150%.

For people with *mild* hemophilia (25% of all cases), spontaneous hemorrhages (bleeding that occurs with no apparent cause) are rare, and joint and deep muscle bleeding are uncommon. Surgical, dental, or other injury or trauma precipitates symptoms that must be treated the same as for *severe* hemophilia.

For those people with *moderate* hemophilia (15% of all people with hemophilia), spontaneous hemorrhage is not usually a problem, but major bleeding episodes can occur after minor trauma. People with *severe* hemophilia comprise 60% of people with hemophilia and may bleed spontaneously or with only slight trauma, particularly into the joints and deep muscle.

Incidence

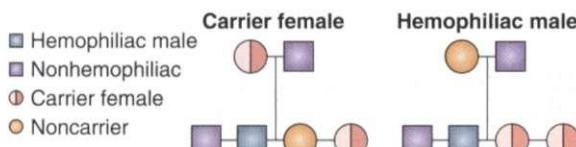
Hemophilia A and B are the most common inherited clotting factor deficiencies,²² with 17,000 people affected by hemophilia A or B (approximately 10,500 with hemophilia A and 3200 with hemophilia B).³¹ Hemophilia primarily affects males without bias for race or socioeconomic group.

Etiologic Factors

The gene responsible for codes for factors VIII and IX are located on the X chromosome, making hemophilia a gender-linked recessive disorder. Since females normally carry two X chromosomes, they only develop hemophilia if both genes are affected, if the normal X gene is inactivated, or if they only have one X chromosome (i.e., Turner's syndrome), making hemophilia rare in females.

Males, on the other hand, only inherit one X chromosome and therefore develop hemophilia since they lack another normal X chromosome to provide these clotting factors (such as most females do). Thus females are the carriers of the abnormality, while males present with the disease (Fig. 14-11).

Every carrier has a one in four chance of having a child with hemophilia. Men with the mutation will pass this on to their daughters (making them carriers), yet their sons will only inherit a normal Y chromosome and not develop hemophilia. Although in two thirds of the cases of hemophilia a known family history is evident, this disorder can occur in families (approximately one third) without a previous history of blood-clotting disorders because of spontaneous genetic mutation. The remaining

**Figure 14-11**

Inheritance patterns in hemophilia for all family members. A woman is definitely a carrier if she is (1) the biologic daughter of a man with hemophilia, (2) the biologic mother of more than one son with hemophilia, or (3) the biologic mother of one hemophilic son with at least one other blood relative with hemophilia. A woman may or may not be a carrier if she is (1) the biologic mother of one son with hemophilia; (2) the sister of a male with hemophilia; (3) an aunt, cousin, or niece of an affected male related through maternal ties; or (4) the biologic grandmother of one grandson with hemophilia. (Reprinted from Beare PG, Myers JL: *Adult health nursing*, ed 3, St Louis, 1998, Mosby.)

rare clotting factor deficiencies are inherited in an autosomal recessive manner.

Pathogenesis

At least 10 proteins called *clotting factors* in the blood must work in a precise order to make a blood clot. Hemophilia A is due to a deficiency of the protein clotting factor VIII (antihemophilic factor), while hemophilia B is a lack of factor IX. These clotting factors are produced by the liver and released into the blood. Factor VIII, once in the plasma, combines with vWF (as previously discussed). Factors VIII and IX are necessary for the formation of thrombin, which converts fibrinogen into fibrin, generating a clot. Clients with these factor deficiencies are unable to produce thrombin and clot.

The genetic pattern of hemophilia is quite different from that of disorders such as sickle cell disease, in which every affected individual has the identical genetic defect. The presence of such variable defects in the same gene accounts for the differences in severity of hemophilia.

Many different genetic lesions cause factor VIII deficiency, such as gene deletions, with all or part of the gene missing, or missense and nonsense mutations, which cause the clotting factor to be made incorrectly or not at all. Not all mutations are inherited; 25% to 30% of cases are due to new mutations. Hundreds of different mutations have been discovered. Most of these mutations are nucleotide substitutions (missense) or small deletions, while one common mutation noted in over 40% of people with severe hemophilia A is a partial inversion. An Internet database is available that documents the mutations in the factor VIII gene.¹²²

Although uncommon, a woman who is a carrier of hemophilia can have very low levels of factors VIII or IX. This is due to the fact that in every cell of the body either the normal X chromosome or the affected X chromosome is randomly inactivated (turned off) in a process called *lyonization*. If the majority of the inactivated chromosomes are the normal X, then the levels of clotting factors may be very low, and such carriers may experience excessive bleeding.

Clinical Manifestations

Clinically, hemophilia A and hemophilia B present with the same symptoms and can only be distinguished by

specific factor assay tests. Unlike most clients with vWD, those with hemophilia manifest delayed and joint and deep muscle bleeding.

Occurrences of bleeding are noted during the newborn period in infants who have hemophilia. The most common instances include immunizations, heel sticks, blood draws, and circumcision. If a child is born to a known carrier, circumcision should not be performed until appropriate tests are completed. As the child grows, bleeding problems will continue to be manifested.

Hematoma formation may result from injections or after firm holding (such as occurs when a child is held under the arms or by the elbow and lifted), excessive bruising from minor trauma, delayed hemorrhage (hours to days after injury) after a minor injury, persistent bleeding after tooth loss, and recurrent bleeding into muscles and joints.

Bruising, bleeding from the mouth or frenulum, intracranial bleeding, hematomas of the head, and hemarthrosis (bleeding into the joints) can occur during early ambulation. By age 3 to 4 years, 90% of children with severe hemophilia have had an episode of persistent bleeding not seen in mild cases.

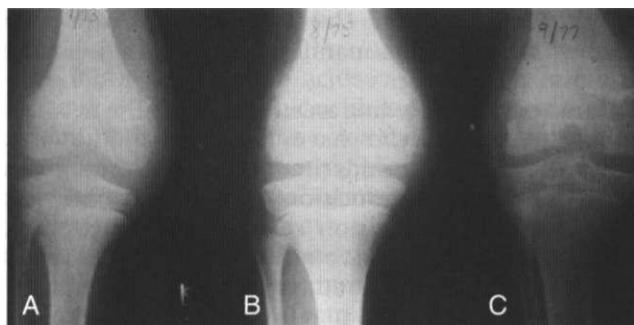
Clients with severe hemophilia often display episodes of spontaneous bleeding (into the joints, muscles, and internal organs) along with severe bleeding with trauma or surgery. Those persons affected with mild to moderate hemophilia do not commonly have spontaneous bleeding but exhibit excessive bleeding with trauma and surgery.

Women with Hemophilia. Women with hemophilia experience excessive uterine bleeding during their menstrual cycle, with possible oozing from the ovary after ovulation mid-cycle. Heavy menstrual flow is often the symptom that initiates a coagulation evaluation or more often is reported but not adequately diagnosed.

Cases have occurred in which a female carrier of the hemophilia gene has abnormal bleeding when the level of clotting factor is low enough to cause significant problems with coagulation, especially after trauma or surgery. Abnormal bleeding from bruising, dental extractions, abortion or miscarriage, complications of pregnancy (e.g., placenta not delivered completely, episiotomy or tearing, prolonged postpartum hemorrhage), nosebleeds, and minor trauma (such as cuts with prolonged oozing) may be overlooked because of the misconception that hemophilia does not occur in women.

Joint. Bleeding into the joint spaces (hemarthrosis) is one of the most common clinical manifestations of hemophilia, significantly affecting synovial joints. The knee is the most frequently affected joint followed by the ankle, elbow, hip, shoulder, and wrist. Bleeding in the synovial joints of the feet, hands, temporomandibular joint, and spine is less common.

Joints with at least four bleeds in 6 months are called target joints, and in children with severe hemophilia, this can occur as a toddler. According to the Centers for Disease Control and Prevention, target joints may occur in as many as 37% of people with hemophilia. When blood is introduced into the joint, the joint becomes distended, causing swelling, pain, warmth, and stiffness.

**Figure 14-12**

Stages of hemophilic arthropathy according to the Arnold-Hilgartner scale. **A**, Stage I (1973). **B**, Stage III (1975). **C**, Stage IV (1977). (Courtesy Mountain States Regional Hemophilia Center, Colorado State Treatment Program, Denver, 1995.)

The synovial membrane responds by producing an increased number of synovial villi and undergoing vascular hyperplasia in an attempt to reabsorb the blood. Blood is an irritant to the synovium, which releases enzymes that break down RBCs and the cell byproducts (e.g., iron). This process causes the synovium to become hypertrophied, with formation of fingerlike projections of tissue extending onto the articular surface.

The mechanical trauma of normal weight-bearing motion may then impinge and further injure the inflamed synovium. Iron in the form of hemosiderin is deposited in the synovium, which impairs the production of synovial fluid. A vicious cycle is established as the synovium attempts to cleanse the joint of blood and debris, becoming more hypertrophic and susceptible to still further bleeding.¹¹ Erosive damage of the cartilage follows these changes in the synovium with narrowing of the joint space (Fig. 14-12), erosions at the joint margins, and subchondral cyst formation. Collapse of the joint, joint sclerosis, and eventual spontaneous ankylosis may occur.

In later stages of joint degeneration, chronic pain, severe loss of motion, muscle atrophy, crepitus, and joint deformities occur. Despite advances in medical management, target joints can progress to advanced arthropathy. This is most commonly seen in people with severe hemophilia. The articular cartilage softens, turns brown (due to hemosiderin), and becomes pitted and fragmented. The inflamed synovium is thick and highly vascularized and can grow over the joint surfaces, becoming pannus.

Eventually, lesions in the deeper layers of cartilage result in subchondral bone breakdown and the formation of subchondral cysts. Osteophyte formation occurs along the edges of the joint (Box 14-7 and Table 14-6). With the destruction of the cartilage, little to no joint space is left. This bone-on-bone contact can lead to significant pain, limitation of motion, joint malalignment, muscle atrophy, functional impairment, and disability.

At this point joint bleeds are rare. For the child, recurrent bleeds into the same joint can lead to growth abnormalities. The epiphyses, where bone growth takes place, are stimulated to grow in the presence of hyperemia

Box 14-7**ARNOLD-HILGARTNER HEMOPHILIC ARTHROPATHY STAGES**

- Staging scheme to classify joint changes seen on radiographs:
- 0 Normal joint
 - I No skeletal abnormalities; soft tissue swelling
 - II Osteoporosis and overgrowth of epiphysis; no erosions; no narrowing of cartilage space
 - III Early subchondral bone cysts, squaring of the patella; intercondylar notch of distal femur and humerus widened; cartilage space remains preserved
 - IV Finding of stage III more advanced; cartilage space narrowed significantly; cartilage destruction
 - V End stage; fibrous joint contracture, loss of joint cartilage space, marked enlargement of the epiphyses, and substantial disorganization of the joints

Reprinted from Arnold WD, Hilgartner MW: Hemophilic arthropathy, *J Bone Joint Surg Am* 59:287-305, 1977.

Table 14-6 Pettersson Classification of Hemophilic Arthropathy

Type of Change	Finding	Score*
Osteoporosis	Absent	0
	Present	1
Enlarged epiphysis	Absent	0
	Present	1
Irregular subchondral surface	Absent	0
	Slight	1
	Pronounced	2
Narrowing of joint space	Absent	0
	<50%	1
	>50%	2
Subchondral cyst formation	Absent	0
	1 Cyst	1
	>1 Cyst	2
Erosions at joint margins	Absent	0
	Present	1
Incongruence between joint surfaces	Absent	0
	Slight	1
	Pronounced	2
Joint deformity (angulation and/or displacement between articulating bones)	Absent	0
	Slight	1
	Pronounced	2

This classification is a joint scoring system based on radiographic findings used to classify and monitor joint changes and damage.

Reprinted from Anderson A, Holtzman TS, Masley J: *Physical therapy in bleeding disorders*, New York, 2000, National Hemophilia Foundation.

*Possible total joint score is 0-13 points.

caused by bleeding. Postural asymmetries may develop (e.g., leg length differences, angulatory deformities, bony enlargement at the affected joint).¹¹

Classification of Hemophilic Arthropathy. Several different classification scales are used to identify progression of hemophilic arthropathy. The Arnold-Hilgartner and Pettersson score classification scales have been in use for many years. With the Arnold-Hilgartner scale, the arthropathy is divided into stages that are assumed to be progres-

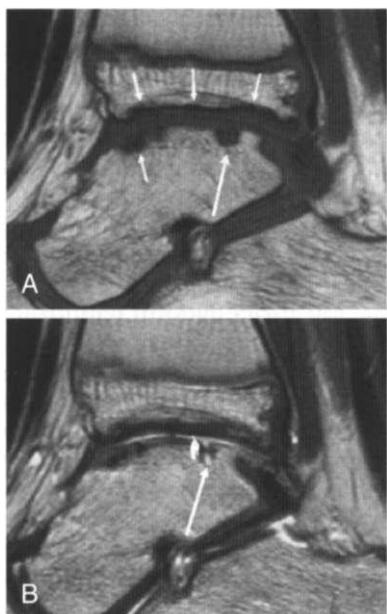


Figure 14-13

MRI of hemophilic arthropathy. **A**, Left ankle of a 9-year-old boy with moderate hemophilia. Sagittal spin echo (SE) T1-weighted sequence. **B**, Sagittal turbo spin echo (TSE) T2-weighted sequence. Cortical irregularity (best seen on T1-weighted image, *small arrows*) is the hallmark of surface erosions. Different types of subchondral cysts have different signal characteristics. In this joint a cyst is discerned in the dorsal part of the talar dome (intermediate signal on T1-weighted image and bright signal on T2-weighted image, *large arrows*), and a focal defect in the overlying cartilage is revealed (joint fluid in defect is bright on T2-weighted image). (Courtesy Björn Lundin, MD, University Hospital of Lund, Sweden.)

sive. With the Pettersson score, a number of specific findings are evaluated and the additive sum of the assigned points is calculated.

In addition, there is now some MRI information being used for classification as well. With improvements in hemophilia care, evaluation of subtle joint changes not readily apparent with conventional radiography has become increasingly important. MRI can visualize effusion, hemarthrosis, synovial hypertrophy and/or hemosiderin deposition, subchondral cysts and/or surface erosions, and loss of cartilage (Fig. 14-13).

Different MRI methods for joint scoring use either a progressive or additive scoring strategy. Using proposed MRI scoring methods, imaging specialists can detect and monitor early joint changes, assess therapeutic outcomes, and further define the pathophysiology of hemophilic joint disease. An in-depth discussion of these techniques is available for readers interested in the specifics.^{114a}

Physical therapists in the United States, Canada, Sweden, and The Netherlands are working collaboratively on an international joint evaluation scale to identify and quantify the early changes seen in hemophilia joint disease. The 11-item scoring tool for assessing joint impairment in boys with hemophilia from 4 to 18 years of age (Hemophilia Joint Health Score) was designed for use in a 10-year prospective study of two types of aggres-

sive treatment in young children with severe hemophilia. Reliability testing of the scoring tool has been published⁷⁸³; validity testing is underway.

Muscle. Muscle hemorrhages can be more insidious and massive than joint bleeding, and although they can occur anywhere, muscle hemorrhages most often involve the flexor muscle groups (e.g., iliopsoas, gastrocnemius, forearm flexors). Intramuscular hemorrhage that is visible in superficial areas such as the calf or forearm will also result in pain and limitation of motion of the affected part. Less-obvious intramuscular hemorrhage such as occurs in the iliopsoas may result in groin pain, pain on extension of the hip, and reflexive flexion of the hip and thigh (see Figs. 16-14 and 16-15).

Other signs and symptoms may include warmth, swelling, palpable hematoma, and neurologic signs such as numbness and tingling. A large iliopsoas hemorrhage can cause displacement of the kidney and ureter and can compress the neurovascular bundle, including the femoral nerve with subsequent weakness; decreased sensation over the thigh and knee in the L2, L3, and L4 distribution; decreased or absent knee reflexes; temperature changes; and even permanent impairment. Iliopsoas bleeds are considered a medical emergency requiring immediate referral to a physician.

Nervous System. In general, compression of peripheral nerves and blood vessels by hematoma may result in severe pain, anesthesia of the innervated part, loss of perfusion, permanent nerve damage, and even paralysis. The femoral, ulnar, and median nerves are most commonly affected.

CNS hemorrhage may include intracranial hemorrhage and, rarely, intraspinal hemorrhage. Intracranial hemorrhages (ICH), or head bleeds inside the skull, in a newborn can occur regardless of the severity of hemophilia and may have long-term consequences such as paralysis, seizures, cerebral palsy, and other neurologic deficits.

Although signs and symptoms of ICH may be dramatic (e.g., seizures, paralysis, apnea, unequal pupils, excessive vomiting, or tense and bulging fontanelles) they are often vague (e.g., crankiness or irritability, lethargy, feeding difficulty), leading to a delay in diagnosis. The lifetime risk of ICH is about 2% to 8% although many are asymptomatic and unreported.¹⁰³ ICH in clients with hemophilia carries a mortality rate of up to 30% when it occurs, making it one of the most common causes of death after HIV.

Inhibitors. With the production of safer factor concentrates, the development of antibody inhibitors (antibodies that destroy the infused factor) poses the most serious complication to hemophilia treatment. Inhibitors occur infrequently, approximately two cases per 1000 person years, but can be serious, causing complications in 20% to 33% of persons who develop an inhibitor.⁶¹¹⁹⁷

The risk of developing an inhibitor does not remain the same during the lifetime of a person with hemophilia, and the appearance of antibodies can be transient or low titers. Factors that increase the risk for developing inhibitors are still under investigation, including significant exposure to factor VIII concentrates (continuous

infusion)¹⁷¹ orthotype of factor VIII product used. Clients with high titers of inhibitors, which decrease therapy efficacy, may receive factor IX concentrates or undergo immune tolerance therapy (frequent infusions of factor VIII).

Transmissible Diseases. Individuals, primarily those with severe hemophilia, who were treated before current purification techniques for factor concentrates (before 1986) may have been exposed to hepatitis B or C and/or HIV. Approximately 50% of people with hemophilia during this period became infected with HIV. No other at-risk group had such a high prevalence. Currently, about 10% to 15% of people with hemophilia have HIV, but since 1986 no further HIV transmission has occurred.

Transmission of hepatitis is equally serious, and about 70% to 90% of people with hemophilia who received clotting factor before the mid-1980s test positive for hepatitis C.¹²⁷ Current improved methods of viral inactivation of factor concentrates through pasteurization and solvent treatment and monoclonal and recombinant technology have resulted in safer products.

Improved screening methods to identify donors with hepatitis have also reduced the risk of hepatitis transmission. As of 1997, there have been no reports of hepatitis A, B, or C transmission through clotting factor treated with these improved processes.⁸³ Up to one third of individuals with a bleeding disorder and hepatitis C were co-infected with HIV, and everyone who was infected with HIV also contracted hepatitis C.¹³¹

The transmission of hepatitis A and parvovirus B19 has also been reduced in plasma-derived products, but hepatitis A can now be prevented by immunization with a vaccine. All newborns with hemophilia now receive the hepatitis B vaccination series, but older clients often have hepatitis B along with its long-term sequelae.

MEDICAL MANAGEMENT

DIAGNOSIS. Effective treatment of hemophilia is based on an accurate diagnosis of the deficient clotting factor and its level in the blood. Diagnosis is not always straightforward, as a variety of factors can confound the test results (e.g., blood type; factor levels can be elevated by stress, hyperthyroidism, and pregnancy, yet decreased in hypothyroidism).

Additionally, cord blood sample at birth may have physiologically low levels of factor IX that only reach adult values by 3 to 6 months of age. Blood tests include assays for clotting factors, CBC (differential and platelets), and activated partial thromboplastin time. Other tests may be added depending on individual variables. It is also important for female relatives of those with hemophilia to identify their carrier status through factor level analysis and DNA testing.

If possible, genetic studies to determine carrier status should be completed before pregnancy. However, prenatal diagnosis of hemophilia A and B is possible if a specific mutation has been found or if linkage studies have provided enough information about carrier status in the family. If one of these two criteria has been met, prenatal diagnosis can be performed, analyzing DNA for specific mutations.

The most common method is through chorionic villus sampling at 10 to 12 weeks of gestation. Ultrasound at 14 to 16 weeks' gestation to determine the gender of the unborn child, amniocentesis at approximately 16 weeks' gestation, percutaneous umbilical blood sampling at 18 weeks' gestation, and preimplantation genetic diagnosis (involving polar body, blastomere, and blastocyst biopsy) are other methods of diagnosis. The advantages and disadvantages of these tests as well as management issues are reviewed in the literature.¹⁰⁴

TREATMENT. Currently no known cure or prenatal treatment for hemophilia exists. Until a medical cure is developed, primary goals for intervention in the case of bleeding episodes are to stop any bleeding that is occurring as quickly as possible and to infuse the missing factors until the bleeding stops.

Treatment for severe forms of hemophilia is recommended to take place in specialized hemophilia treatment centers across the United States and its territories. In these centers the specialized care required can be provided through a multidisciplinary team approach with appropriately trained and experienced health care providers. Treatment at a hemophilia treatment center has been shown to minimize disability, morbidity, and mortality rates.^{3,11,176}

Factor replacement therapy, given intravenously, is currently the mainstay of hemophilia treatment. Treatment with infusion of the missing factor at a 25% to 30% plasma factor level is recommended for minor bleeding; at least a 50% level is recommended before minor surgery and dental extractions or in case of minor injury, and it may be recommended before physical or occupational therapy interventions. Infusion at 75% to 100% may be recommended before major surgery or in the case of life-threatening bleeding.

Permanent prophylaxis of recombinant factors for severe hemophilia (i.e., factor infusion given on a regularly scheduled basis) to maintain blood factor levels in the moderate range is now widely accepted. Most clients should receive infusions on at least a weekly basis, although questions remain of when to initiate prophylaxis (first joint bleed vs. early age).¹ Prophylaxis therapy is very expensive, but treatment of target joints can increase the cost as much as twofold.⁸⁸ Uncertainty exists as to whether prophylaxis helps prevent joint disease, and studies are pending completion that would help answer these questions.

Most factor VIII concentrates are produced using recombinant techniques to provide virus-free products. First-generation factor VIII products contain animal or human plasma proteins, while second-generation concentrates contain these proteins in the cell culture medium but not in the final product. Third-generation products do not contain animal or human plasma proteins in either the cell culture medium or the final product.

Methods used prior to the availability of recombinant technology to manufacture factor VIII concentrates utilized plasma pooled from thousands of donors that was then purified for factor VIII. This purified concentrate was

treated to deplete viruses (heating in an aqueous solution, treated by a solvent detergent, or immunoaffinity purification). While this type of product is still available and there have been no reports of clients being infected with hepatitis B or C or HIV, the risk remains that these pooled-plasma products could possibly lead to viral transmission. This possible increased risk of transmitting a virus makes recombinant concentrates the recommended treatment of choice.

With the use of recombinant factor, human viruses are not easily transmitted through factor use, and the possibility of any other contaminants being transmitted is unlikely. Product manufacturers are continuing to develop products with a higher recovery level and to increase the efficiency of the factor products (i.e., percent of factor protein that remains active in the blood after infusion; the higher the level of a factor product's recovery, the more efficient the product).

Persons with mild hemophilia can use the drug desmopressin when possible (see above section under vWD). If this medication does not provide adequate hemostasis or the client is pregnant or younger than 2 years, factor VIII concentrates should be utilized.

Treatment for clients with hemophilia B consists of factor IX concentrates. Recombinant factor IX concentrates do not use animal or human plasma proteins in the purification process, making the product safe from viruses. Pooled plasma-derived factor IX products are available, and like the factor VIII concentrates from pooled plasma, undergo a viral-depletion step. However, due to the safety factor of recombinant technology, recombinant factor IX concentrate is the medication of choice.

For those clients who developed chronic hepatitis C from the use of blood products prior to the mid 1980s, progression and treatment response appear to be similar to those people without hemophilia.^{109,127} Treatment and prognosis for hepatitis are discussed in Chapter 17.

Administration of the hepatitis A and hepatitis B vaccines is recommended for anyone with chronic hepatitis C because of the potential for increased severity of acute hepatitis superimposed on existing liver disease. Younger children are now vaccinated against hepatitis A and B, but no vaccine is available for hepatitis C at this time. Although treatment for hepatitis B is available, liver transplantation may be required. Liver transplantation is successful in people who have hemophilia with advanced liver disease but is often unavailable.

Comprehensive medical management of hemophilia may involve the use of drugs to control pain in acute bleeding and chronic arthropathies. People with hemophilia cannot use the common pain relievers aspirin or ibuprofen because these agents inhibit platelet function. More precisely, platelets do form an initial clot, but factor VIII or IX is unavailable to stabilize the clot.

Some medications contain derivatives of aspirin and must be used cautiously. Corticosteroids are used occasionally for the treatment of chronic synovitis. Acetaminophen (Tylenol) is a suitable aspirin substitute for pain control, especially in children. Clients who have had continued target joint bleeding often require surgical

synovectomy or radioactive synovectomy to decrease bleeding and reduce the rate of destruction of the joint. Clients have also demonstrated stable or improved range of motion following these procedures.^{55,56}

Physical therapy intervention (see Special Implications for the Therapist: Hemophilia in this chapter) has been effective in reducing the number of bleeding episodes through protective strengthening of the musculature surrounding affected joints, muscle reeducation, gait training, and client education. Physical therapy is used during episodes of acute hemorrhage to control pain and additional bleeding and to maintain positioning and prevent further deformity.

Gene therapy is still in experimental stages but appears very promising. When successful, gene therapy will deliver a normal (unaffected) copy of a gene into a target cell that contains a defective gene. Human trials are underway for hemophilia A and B using a variety of different delivery techniques. In fact, hemophilia is considered a model disease for treatment with gene therapy because it is caused by a single malfunctioning gene, and only a small increase in clotting factor could provide a great benefit.¹¹⁷

PROGNOSIS. Years ago most men with hemophilia died in their youth. Currently, the majority of deaths in persons with hemophilia are viral related (hepatitis B and C, HIV), yet with improved diagnosis and significantly improved treatment (including safety), they can reach a longer life expectancy.¹⁵²

Tremendous improvement has been made in carrier detection and prenatal diagnosis to provide early treatment and prevent complications. Gene therapy for hemophilia A and B, now in clinical trials, holds promise of a cure. Additionally, home infusion therapy provides immediate treatment with clotting factor for joint and muscle bleeds recognized early. Early treatment has significantly reduced the morbidity formerly associated with hemophilia.

Medical treatment prolongs life and improves quality of life associated with improved joint function, but HIV and hepatitis can significantly reduce longevity and quality of life. Fortunately, improvements in blood screening tests, more stringent donor exclusion criteria, improved viral inactivation methods, and the introduction of recombinant hemophilia therapies have combined to dramatically reduce the rate of new bloodborne viral infections among people with hemophilia, especially those children born in the last decade.

From the period of 1979 to 1998, the death rate of persons with hemophilia A and HIV decreased 78%.³⁵ Much of this decrease was related to improved HIV therapy. With the advent of safer factor concentrates, there is a trend of increased life expectancy for people with hemophilia. Those people with hemophilia but without HIV or hepatitis have a life expectancy near normal.

ICH still remains a deadly complication of hemophilia, but prophylaxis treatment and improved understanding of the signs and symptoms associated with ICH may help to improve outcomes.

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-12

Hemophilia**PREFERRED PRACTICE PATTERNS**

4B: Impaired Posture (joint deformity)

4D: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Connective Tissue Dysfunction

5A: Primary Prevention/Risk Reduction for Loss of Balance and Falling

5C: Impaired Motor Function and Sensory Integrity Associated with Nonprogressive Disorders of the Central Nervous System: Congenital Origin or Acquired in Infancy or Childhood (CNS involvement)

5F: Impaired Peripheral Nerve Integrity and Muscle Performance Associated with Peripheral Nerve Injury (nerve compression)

6F: Impaired Ventilation and Respiration/Gas Exchange Associated with Respiratory Failure (coagulation defect)

Physical therapy intervention for individuals with hemophilia has undergone a drastic change. Two decades ago, everyone in the hemophilia community had joint disease in varying degrees of severity. Today treatment protocols are more aggressive, with more frequent infusions given at younger ages, resulting in less joint damage.³⁶

Many children with hemophilia are growing up without having a single joint bleed. The focus has shifted from rehabilitation to prevention; therapists are an important health care professional in helping these individuals lead normal, active lives.³⁶ Only a brief discussion of treatment for the adult or child with hemophilia can be included in this text. For a more detailed examination, evaluation, and interventions, the reader is referred to other more specific references.^{11,26,78,130}

Hemophilia and Exercise

A regular exercise program, including appropriate sports activities, resistance training, cardiovascular/aerobic training, and therapeutic strengthening and stretching exercises for affected extremities, is an important part of the comprehensive care of the individual with hemophilia. The therapist can help individuals with hemophilia identify, seek out, and enjoy physical activity, exercise, and sport participation that provide benefits that outweigh the risks.⁷⁸

Exercise not only promotes physical wellness in the form of improved work capacity, it protects joints, enhances joint function, and is beneficial for decreasing the frequency of bleeds and has been shown to temporarily increase the levels of circulating clotting factor in individuals with a factor VIII deficiency.¹³² Immobilization of joints can lead to deterioration of muscles, which in turn leads to joint instability and repeated bleeding and premature development of arthropathy.^{126,181}

Growing evidence suggests that exercise, coupled with a healthy diet, may boost the immune system of people with hemophilia who also have HIV and/or are

living with hepatitis C.¹⁹⁶ The therapist can be instrumental in helping the person with hemophilia to individualize an exercise or sports activity plan with specific but realistic goals and a schedule with alternating exercises (cross-training).

While many factors related to joint bleeding are fixed, one risk factor that can be modified by the therapist is the body mass index. Clients with more severe disease develop joint problems earlier with accompanying range-of-motion problems. An increased body mass index also increases the risk of limited joint range-of-motion and may be a modifiable risk factor in clients with hemophilia.^{17,63}

An overall therapy program includes client education early on for family, client, school personnel, and coaches for prevention, conditioning, and wellness. Specific guidelines are available including all age levels from infants, toddlers, and preschoolers to adults, including sports safety information and the categorization of sports and activities by risk.^{11,130}

For older children and adolescents, selecting a sport with a good chance of success and adequate preparation (e.g., stretching and flexibility, conditioning including strength and weight training, endurance including an aerobic component, and possibly infusion before participation) for the sport is crucial.

The National Hemophilia Foundation has mapped out categories of activity that are safe to participate in for anyone with hemophilia along with precautions for some forms of exercise and contraindications to others (Table 14-7).

Category 1 involves primarily aerobic activities that are considered "safe" for most individuals with hemophilia. Category 1 activities build muscles to protect joints and help decrease the frequency of bleeds. Gaining flexibility and core strength through category 1 activities is a prerequisite for anyone with hemophilia before participating in category 2 activities.

Category 2 activities include sports and recreational activities in which the physical, social, and psychologic benefits of participation outweigh the risks. Individuals with severe hemophilia may have to avoid category 2 activities. Category 3 activities should be avoided by anyone with hemophilia; they are dangerous even for people without hemophilia. The risks outweigh the benefits.

Although it is obvious that some bleeding may result from participation in a sport, fewer bleeding episodes occur when children engage in physical activities on a regular basis than when they are sedentary. When a particular sport or activity is often followed by bleeding, then that activity should be reevaluated. A joint that requires multiple infusions to stop bleeding, remains symptomatic, or has persistent synovitis is not likely to withstand the stresses of a sport that relies on that joint.¹³⁰

As orthopedic problems occur, a problem-oriented program is developed specific to the pathology. Generally, a therapy program includes exercises to strengthen muscles and improve coordination; methods to prevent and reduce deformity; methods to influence abnormal muscle tone and pathologic patterns of

Table 14-7 Categories of Activities Based on Risk

Category 1 (Safest)	Category 2 (Moderately Safe)	Category 3 (Potentially Dangerous)
Archery	Baseball	All-terrain vehicle use
Badminton	Basketball	Boxing
Bicycling	Bowling	High diving (competitive)
Dancing	Cross-country skiing	Football
Fishing	Diving (recreational)	Hockey
Frisbee	Dog sledding	Lacrosse
Golfing	Gymnastics	Motorcycling
Hiking	Horseback riding	Racquetball, handball
Ping pong	Ice skating	Rock climbing, rappelling
Snow shoeing	Jogging	Rugby
Swimming	Martial arts	Wrestling
Tai chi	Mountain biking	Power lifting, competitive weight lifting
Walking	River rafting	
Low-impact workout machines	Roller skating/blading	
	Rowing/crew	
	Running	
	Skiing (downhill or cross country)	
	Snowboarding	
	Snowmobiling	
	Soccer	
	Tennis	
	Track and field	
	Volleyball	
	Water skiing	
	Weight lifting	

This is not an exhaustive list of possible activities but provides a guideline to use when assessing activities for safety.

Modified from National Hemophilia Foundation: *Hemophilia, sports, and exercise*, New York, 2007, The Foundation.

movement; techniques to decrease pain; functional training related to everyday activities; special techniques such as manual traction and mobilization; massage; and physiotechnical modalities such as cold, heat (including ultrasound), and electric modalities.

Aquatic therapy is an excellent modality, especially for chronic arthropathy. The buoyancy of the water allows for ease of active movements across joints without the compressive force induced by gravity, thus decreasing pain. Water's density creates a resistive force to allow muscle strengthening, and the hydrostatic pressure can help reduce swelling.¹¹

Guidelines to Strength Training

In the past people with bleeding disorders were told to avoid strenuous exercise and any kind of weight training to avoid the risk of bleeding episodes. Today we know that a well-planned exercise program can be extremely beneficial to all individuals with a bleeding disorder. Weight training is still approached with caution as overly strenuous free-weight lifting can still cause micro-tears in the muscles and intramuscular bleeds.^{7,12,13}

Strength training, also known as resistance training, builds muscle, increases strength, stabilizes joints, improves circulation, and potentially reduces the risk of injury and spontaneous bleeding episodes. It is not body building, power lifting, or competitive weightlifting; these activities should be avoided.

The importance of warm-up and cool-down periods should be emphasized. Little or no weight is used until the individual can complete 10 to 15 repetitions with proper form. Weight or resistance can be gradually increased by 5% to 10% when the first phase of 10 to 15 repetitions is easy. The client should be reminded never to attempt to lift maximal weight.^{7,8}

As with all strength training, it is best to utilize full pain-free range of motion slowly and with good breathing throughout the cycle of contraction and relaxation. Maintain adequate hydration at all times. Adolescents must especially be reminded that pain is a red flag to stop and seek help. Most injuries result from improper form and performing the exercise too fast. Any time an individual of any age with hemophilia experiences joint trauma or injury, strength training may have to be discontinued and gradually reintroduced after healing occurs.⁷

Maintaining Joint Range of Motion

The therapist and client must be alert to recognize any signs of early (first 24 to 48 hours) bleeding episodes (Table 14-8). Providing immediate factor replacement to stop the bleeding and following the RICE principle (Table 14-9) to promote comfort and healing are two goals for treating an acute joint (hemarthrosis) or muscle bleed (intramuscular hemorrhage).

The joint range of motion can be measured during this acute episode in the pain-free range but should not be strength tested. Elastic wraps, splints, slings, and/or assistive devices may be necessary and a tolerance and/or weaning schedule established.¹¹ Static or dynamic night splints may be used to apply a low-load stretch to a muscle shortened because of an underlying condition such as synovitis or articular contracture.

A static splint made of plaster, synthetic casting materials, or thermoplastic splinting materials holds the joint in a single position. The material is molded to the extremity, then hardens, and straps are applied to keep it in place on the extremity. A static splint does not bend or straighten the joint. It must be remolded or remade as the individual gains range of motion.^{9,13}

A dynamic splint applies a small amount of pressure (1 to 2 lbs) to stretch a joint over a long period. The individual can still bend and straighten the joint and the therapist can adjust the amount of load applied as needed. There is less irritation and fewer bleeds with the dynamic splint.

Repeated bleeds in the same area can cause a muscle to shorten, limiting joint range of motion. Individuals with inhibitors or limited access to treatment are at increased risk for this type of problem. Night splints may be a good option for people who have muscle

Continued.

Table 14-8 Clinical Signs and Symptoms of Hemophilia Bleeding Episodes

Acute Hemarthrosis	Muscle Hemorrhage	GI Involvement	CNS Involvement
Aura, tingling, or prickling sensation	Gradually intensifying pain	Abdominal pain and distention	Impaired judgment
Stiffening into the position of comfort (usually flexion)	Protective spasm of muscle	Melena (blood in stool)	Decreased visual and spatial awareness
Decreased range of motion	Limitation of movement at the surrounding joints	Hematemesis (vomiting blood)	Short-term memory deficits
Pain/tenderness	Muscle assumes a position of comfort (usually shortened)	Fever	Inappropriate behavior
Swelling	Loss of sensation	Low abdominal/groin pain from bleeding into wall of large intestine or iliopsoas muscle	Motor deficits: spasticity, ataxia, abnormal gait, apraxia, decreased balance, loss of coordination
Protective muscle spasm		Hip flexion contracture from spasm of the iliopsoas muscle secondary to retroperitoneal hemorrhage	
Increased warmth around joint			

Modified from Goodman CC, Snyder TE: *Differential diagnosis for the physical therapist: screening for referral*, ed 4, Philadelphia, 2000, WB Saunders.

Table 14-9 Management of Joint and Muscle Bleeds

Joint: Acute Stage	Joint: Subacute Stage	Muscle
Factor replacement	Factor replacement (if indicated)	Factor replacement
RICE	Progressive movement and exercises	RICE
Pain-free movement	Wean splints and slings	Appropriate weight-bearing status; bed rest for iliopsoas bleed
Pain medication	Progressive weight bearing	Progressive movement

RICE, Rest, ice, compression (applying pressure to the area for at least 10 to 15 min), and elevation (immobilizing and elevating the body part above the heart while applying ice).

Modified from Anderson A, Holtzman TS, Masley J: *Physical therapy in bleeding disorders*, New York, 2000, National Hemophilia Foundation.

contractures that are not responding to other treatment interventions. The desired effect can be obtained in 6 to 8 weeks for individuals who do not have an inhibitor. For those clients with inhibitors, night splinting can take much longer (6 months to 1 year).

⁹³ Serial casting may be a better choice for clients with longstanding problems; either splinting or casting should be used before resorting to surgery.^{68a,162}

The therapist must watch for leg length discrepancy as a long-term result of joint arthropathy. Even minor discrepancies can affect standing posture and gait mechanics and contribute to low back pain and other lower quadrant impairments. Shoe lifts in conjunction with appropriate prophylactic therapy and exercise can be effective.^{75,92}

Specific Exercise Guidelines

Initiation of exercise after a bleed must be delayed, and rehabilitation progress is typically slower for individuals with factor VIII and factor IX deficiency who develop factor inhibitors. Prognosis for full return of function is diminished in such cases. In all cases of joint bleed, the use of heat is contraindicated; if used, hydro-

therapy or aquatic intervention must be performed in comfortable but not hot temperatures to avoid blood vessel dilation.

When active bleeding stops, isometric muscle exercise should be initiated to prevent muscular atrophy. This exercise is especially critical with recurrent knee hemarthroses to prevent the visible atrophy of the quadriceps femoris muscle. As pain and edema diminish, the client should begin gentle active range-of-motion exercises followed by slowly progressing strengthening exercises when the joint is pain free through its full range. In the case of an iliopsoas bleed, when ambulation is resumed, crutches and toe-touch weight bearing are initiated. Active movement should be performed in a pain-free range and progressed very slowly.¹¹

For all muscles, as the strengthening program is progressed, strengthening aids such as elastic bands or tubing and cuff weights can be used before transitioning to weight equipment. Preadolescents should avoid using high-weight lifting machines.

Postbleed exercise should also take into consideration any damage that may have occurred to the joint, such as ligamentous or capsular stretching. Closed chain and other exercises to restore proprioception should be incorporated into the rehabilitation program.¹¹

As a prophylactic measure, clients with severe hemophilia generally need to infuse with clotting factor when participating in a strengthening program. With careful supervision and progression of the exercise program, the individual can progress to aerobic activities.

In some individuals, increased stress levels result in increased frequency of spontaneous bleeding. Biofeedback may be considered especially helpful for these clients who experience spontaneous bleeding during emotional upsets and periods of depression. Biofeedback can also be used for muscle retraining or relaxation techniques to control muscle spasm and allow range of motion.

The Older Adult with Hemophilia

Life expectancy has increased dramatically with modern treatment for hemophilia. Although today's

treatments have reduced the number and severity of joint bleeds, middle-aged and older adults with hemophilia did not have the benefit of powdered concentrates and prompt home care.

As children they were hospitalized and/or bed bound with casts, packed in ice while whole blood was administered slowly by intravenous drip. It took days for their levels to go up. Before factor replacement it could take weeks to get a joint bleed under control. The consequence of this type of treatment was contracted joints and severe arthritis.²⁷

Today's older adult still may not have quick and easy access to factor replacement. Mobility impairments can make it difficult, if not impossible, to get to a hemophilia treatment center. Loss of fine motor control or the onset of tremors makes self-care at home equally problematic. Adults with hemophilia are not spared from other health care concerns such as diabetes, heart disease, stroke, or cancer. The management of comorbidities may be complicated even more by the bleeding disorder.

The therapist can begin education about long-term planning with middle-aged clients. Introducing the idea of home modifications to improve accessibility should begin early. The importance of staying active cannot be overemphasized. All older adults find that recovery time and rehabilitation take longer as they advance through the decades. Resuming normal activities after injury, surgery, or health conditions that set them back is extremely important.²⁷

It is also important to keep educating young clients who are noncompliant with their treatment and ignore recommendations. These individuals likely will have problems in the future similar to those experienced by today's older adult population, who did not have the benefit of modern treatment interventions.

The same is true for young adults during the college years or transitioning from living at home with adult supervision during high school to living on their own independently. For many people with bleeding disorders, this is the first time they will assume "ownership" of their disease.¹²¹ Maintaining physical fitness at every stage of life is a key part of management for hemophilia.

Orthopedic/Surgical Interventions

Whereas factor replacement can be used to control bleeding associated with surgery, any operative procedure is complicated for individuals who develop inhibitors. Sometimes, even with optimal infusion therapy and aggressive hemophilia care, a joint becomes a chronic problem. In such cases orthopedic or surgical intervention may be indicated to alleviate pain and deformity and to restore the joint to a more functional state. This may include prescription for an orthosis or a splint or serial casting to increase range of motion. Joint replacement (arthroplasty) is now a treatment option as well.

Synovectomy (removal of the joint synovium) is recommended to stop a target joint from its cycle of bleeding. This procedure is not usually done to improve range of motion or to decrease pain, but rather to

prevent further damage to the joint caused by bleeding. Arthroscopic synovectomy is best performed before joint degeneration has progressed beyond stage II on the Arnold-Hilgartner scale (see Box 14-7).

Injection of a radioactive isotope (referred to as *isotopic synovectomy* or *synoviorthesis*, usually ³²P in the United States), which causes scarring to the synovium to arrest bleeding, is an option. This procedure has unique advantages and disadvantages and may be more appropriate for one type of client than another.⁵⁵⁻⁵⁶

Arthroplasty (joint replacement) is indicated when a joint shows end-stage damage and has become extremely painful. Client age, range of motion, and level of pain and function are determinants as to the timing of this procedure. Knees, hips, and shoulders are most commonly helped through arthroplasty, with restoration of pain-free joint movement.

The benefits of a 6-week preoperative physical therapy program (prehabilitation) combined with 6 weeks of postoperative rehabilitation have been demonstrated. An individually tailored and supervised program to increase range of motion and muscle strength enables rapid mobilization and recovery of function while minimizing the risk of bleeding.¹⁸⁰

Long-term results of joint replacement are still under investigation. Mechanical survival of the implant is reported as good or excellent for 80% of knees, but the incidence of late infection (months to years later) resulting in implant failure remains high (16%).^{134,174}

Arthrodesis (joint fusion) may be performed in a joint with advanced, painful arthropathy untreatable by arthroplasty. Joint fusion can relieve or eliminate pain to provide improved quality of life, but it also causes permanent loss of joint motion. Arthrodesis can be a very effective way to provide the individual a more stable base for weight-bearing activities.

Osteotomy (removal of a section of bone) may be done to correct angular deformities in a joint and may be considered before arthroplasty to reduce the stresses placed on a joint caused by poor alignment. Other less-common interventions may include excision of a hemophilia pseudotumor or removal of cysts or exostoses.

The Person with Hemophilia and HIV

It is important for anyone with both hemophilia and HIV to maintain optimal care of their musculoskeletal systems during and between bleeding episodes. It is especially important in the presence of chronic arthropathy and HIV or AIDS to maintain joint function through nonsurgical means, especially exercise.

Surgery may be contraindicated if the risk of infection is too great (e.g., when the CD4 cell count is less than 200). Activities such as tai chi and yoga provide stretching, strengthening (including weight bearing), and a mild aerobic component. Aquatics or swimming must be approached with caution because of the potential for transmission of *Cryptosporidiosis* oocysts, which cause infection in immunocompromised individuals.¹¹

Box 14-8**CAUSES OF THROMBOCYTOPENIA****Increased Platelet Destruction**

- Immune thrombocytopenic purpura
- Drug induced, immune related (e.g., heparin, sulfa drugs)
- Thrombotic microangiopathy (also called thrombotic thrombocytopenic purpura)
- DIC
- Vasculitis
- Bypass during heart surgery
- Mechanical heart valve
- Splenic sequestration
- vWD

Decreased Platelet Production

- Bone marrow infiltration (metastatic neoplasms, leukemia, lymphoma, myeloma)
- Bacterial infections (mycobacteria)
- Viral infections (HIV, cytomegalovirus, hepatitis C)
- Nutritional deficiencies (folate, B12)
- Aplastic anemia
- Myelofibrosis
- Drug induced, not immune related (e.g., alcohol, chemotherapy agents, chloramphenicol)

Thrombocytopenia

Thrombocytopenia, a decrease in the platelet count below 150,000/mm³ of blood, is caused by inadequate platelet production from the bone marrow, increased platelet destruction outside the bone marrow, or splenic sequestration (entrapment of blood and enlargement in the spleen). Thrombocytopenia is a common complication of leukemia or metastatic cancer (bone marrow infiltration) and aggressive cancer chemotherapy (cytotoxic agents). Thrombocytopenia may also be a presenting symptom of aplastic anemia (bone marrow failure); other causes are listed in Box 14-8.

Mucosal bleeding is the most common event and occurs by simply blowing the nose or brushing the teeth. Other sites of mucosal bleeding may include the uterus, GI tract, urinary tract, respiratory tract, and brain (ICH). Symptoms include epistaxis (frequent and difficult to stop), petechiae and/or purpura in the skin (especially the legs) and oropharynx, easy bruising, melena, hematuria, excessive menstrual bleeding, and gingival bleeding.

Diagnosis requires laboratory examination of blood and perhaps bone marrow (if clinically indicated) to confirm the diagnosis. Treatment depends on the precipitating cause (e.g., treatment of underlying leukemia or cessation of cytotoxic drugs until platelet count elevates).

Other treatment methods for immune-related thrombocytopenia (e.g., immune thrombocytopenic purpura) may include use of corticosteroids (e.g., prednisone); intravenous immune globulin and Rh_s(D); splenectomy; monoclonal antibody agents (e.g., rituximab); and plasmapheresis, a procedure that removes blood from the

body, separates the portion containing the antiplatelet antibodies, and then returns the cleansed blood to the body. Newer drugs, thrombopoietic agents, are being tested to provide medications with fewer adverse events.²⁵

Transfusions with platelets are avoided in clients with immune thrombocytopenic purpura unless severe bleeding occurs. However, clients with a secondary cause for thrombocytopenia (e.g., acute leukemia treatment and severe complications of chemotherapy agents that cause thrombocytopenia) may require platelet transfusions for bleeding and/or counts less than 15,000/mm³.

The prognosis is variable depending on the underlying cause; it is poor when associated with leukemia or aplastic anemia but good with conditions amenable to treatment.

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-13***Thrombocytopenia*****PREFERRED PRACTICE PATTERN**

4D: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Connective Tissue Dysfunction (hemarthropathy)

Thrombocytopenia can cause bleeding into the muscles or joints, and the therapist may encounter the severe consequences of this condition. The therapist must be alert for obvious skin or mucous membrane symptoms of thrombocytopenia such as severe bruising, external hematomas, and the presence of petechiae.

Such signs usually indicate a platelet level below 150,000/mm³. Instruct the client to watch for signs of thrombocytopenia and when noted to immediately apply ice and pressure to any external bleeding site. They should avoid aspirin and aspirin-containing compounds without a physician's approval because of the risk of increased bleeding.

Strenuous exercise or any exercise that involves straining or bearing down could precipitate a hemorrhage, particularly of the eyes or brain. See Table 40-9 for specific exercise guidelines for thrombocytopenia. Exercise prescription is highly individualized and should take into account intensity, duration, and frequency appropriate for the individual's condition, age, and previous activity level.

Blood pressure cuffs and similar devices must be used with caution. When used, elastic support stockings must be thigh high, never knee high. Mechanical compression with a pneumatic pump and soft tissue mobilization are contraindicated unless approved by the physician. Practice good handwashing (see Boxes 8-4 and 8-5) and observe carefully for any signs of infection (see Box 8-1). (See also Special Implications for the Therapist: Anemia in this chapter.)

Effects of Aspirin and Other Nonsteroidal Antiinflammatory Drugs on Platelet Function

Acquired disorders of platelet function can occur through the use of aspirin and other NSAIDs that inactivate platelet cyclooxygenase. This key enzyme is required for the production of thromboxane A₂, a potent inducer of platelet aggregation and constrictor of arterial smooth muscle.

A single dose of aspirin can suppress normal platelet aggregation for 48 hours or longer (up to 1 week) until newly formed platelets have been released. Platelets are anucleated, and once aspirin irreversibly inhibits cyclooxygenase, the platelet is unable to synthesize new enzyme and remain inactive for the rest of its lifespan.

NSAIDs have less-potent antiplatelet effects than aspirin since they reversibly inhibit cyclooxygenase. Symptoms from this phenomenon are mild and may consist of easy bruising and bleeding, usually confined to the skin. The use of aspirin or NSAIDs is usually contraindicated before any surgical procedure. Prolonged oozing following dental procedures or surgery may occur.

Disseminated Intravascular Coagulation

Definition and Overview

Disseminated intravascular coagulation (DIC), sometimes referred to as *consumption coagulopathy*, is a thrombotic disease caused by overactivation of the coagulation cascade (i.e., normal coagulation gone awry).

It is an acquired disorder with diffuse or widespread coagulation occurring within arterioles and capillaries all over the body. DIC is actually a paradoxical condition in which clotting and hemorrhage occur simultaneously within the vascular system.

Uncontrolled activation occurs in both the coagulation sequence, causing widespread formation of thromboses (clots) in the microcirculation, and the fibrinolytic system, leading to widespread deposition of fibrin in the circulation. Hemorrhage may occur in the kidneys, brain, adrenals, heart, and other organs.

Incidence and Etiologic Factors

DIC is common, particularly after shock, sepsis, obstetric/gynecologic complications, cancer (e.g., acute leukemia, colon cancer, pancreatic carcinoma), and massive trauma. The oncology client may develop this syndrome as a result of either the neoplasm itself or the treatment for the neoplasm. DIC may occur as a result of a variety of predisposing conditions that activate the clotting mechanisms (see Fig. 6-14).

Pathogenesis

In the normal steady state there is a balance between the procoagulant and the anticoagulant factors, which keeps blood flowing. When DIC occurs there is serious disruption of this system, increasing the procoagulant factors but decreasing the anticoagulant factors.

Lipopolysaccharide, a complex molecule, stimulates endothelial cells to produce tissue factor, which then activates the coagulation system. Fibrinogen is converted to fibrin, which forms thrombi in the small vessels. Normally, in response to the up-regulation of the coagulation system, the anticoagulants counter the response. When overwhelming coagulation occurs, these anticoagulant factors are reduced, allowing for unregulated coagulation.

Sepsis, for example, lowers the levels of anticoagulants such as protein C, protein S, and antithrombin III, further reducing the body's ability to respond to the coagulation process. Hypercoagulable reactions are mediated by cytokines, including TNF- α and IL-6. Although fibrinolysis is activated in this process by the action of TNF- α , its activity is impaired by the inhibitory effect of plasminogen activator inhibitor-1.¹⁸⁶

The following three pathogenetic steps are observed and illustrated in Figure 6-14. Hemostasis is initiated by (1) endothelial or tissue injury (exposure of tissue factor), (2) activation of factor XII, and (3) direct activation of factor X. *Damage to the endothelium* (e.g., from sepsis, hypoxia, cardiopulmonary arrest) can precipitate DIC by activating the intrinsic clotting pathway, whereas *tissue injury* (e.g., obstetric complications, malignant neoplasm, infection, burns) can precipitate DIC by activating the extrinsic pathway. *Release of factor XII* in the circulation facilitates the *activation of factor X* (proteolytic effect).

Once either clotting cascade (intrinsic or extrinsic) is stimulated, widespread coagulation occurs throughout the body, leading to thrombotic events within the vasculature. The normal inhibitory mechanisms become overwhelmed so that clotting can occur unrestricted. As a result of the widespread clotting that occurs, the clotting factors become used up and hemorrhage occurs. This leads to the two primary pathophysiologic alterations of DIC: thrombosis in the presence of hemorrhage.

Clinical Manifestations

The tendency toward excessive bleeding can appear suddenly, with little warning, and can rapidly progress to severe or even fatal hemorrhage. Thrombosis may occur in various sites distant to the tumor or its metastases.

Signs of DIC include continued bleeding from a venipuncture site, occult and internal bleeding, and, in some cases, profuse bleeding from all orifices. Other less-obvious and more easily missed signs are generalized sweating, cold and mottled fingers and toes (due to capillary thrombi and hypoxia), and petechiae.

MEDICAL MANAGEMENT

DIAGNOSIS, TREATMENT, AND PROGNOSIS. Diagnosis is made based on clinical presentation in combination with client history; laboratory blood tests can aid in the diagnosis (e.g., D-dimer test, coagulation tests).

Treatment is always directed toward the underlying cause and must be highly individualized according to the person's age, nature and origin of DIC, site and severity of hemorrhage or thrombosis, and other clinical parameters. The hemorrhagic or thrombotic symptoms may be alleviated by appropriate blood product replacement or

anticoagulants, but the coagulopathy will continue until the causative process is reversed.

Researchers are investigating strategies aimed at inhibiting coagulation activation with protein C, antithrombin, and tissue factor pathway inhibitor.²⁰⁶

The mortality rate for DIC is no longer high with early recognition and treatment, but DIC does contribute to significant morbidity and some mortality as it occurs often with sepsis and cancer. Acute DIC can be fatal depending on the response to treatment.

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-14

Disseminated Intravascular Coagulation

PREFERRED PRACTICE PATTERNS

Preferred practice patterns are not applicable in this condition. DIC is a medical problem that, when present as a co-morbidity, requires consideration regarding precautions during any intervention, but it is not a condition requiring primary PT or OT intervention.

Clients with DIC are treated by the therapist in oncology or intensive care units. DIC is either the consequence of malignancy or the end result of multisystem organ failure after trauma affecting multiple systems (e.g., severe trauma or burns).

Clients are in critical condition and require bedside care. Care must be taken to avoid dislodging clots and cause new onset of bleeding. Monitor the results of serial blood studies, particularly hematocrit, Hb, and coagulation times prior to any intervention. To prevent injury, bed rest during bleeding episodes is required.

Hemoglobinopathies

Several diseases are a result of an abnormality in the formation of Hb. Because Hb is essential for life, anomalies in the shape, size, content, or oxygen-carrying capacity can lead to severe problems. Sickle cell disease and thalassemia are two hemoglobinopathies with potential for serious complications and are discussed further.

Hereditary spherocytosis, hereditary elliptocytosis, hereditary stomatocytosis, and pyropoikilocytosis are rare diseases that occur because of defects in the erythrocyte membrane that cause premature clearance of RBCs (hemolysis). Glucose-6-phosphate dehydrogenase deficiency also leads to hemolysis. Discussions of these diseases can be found elsewhere.

Sickle Cell Disease

Overview and Incidence. *Sickle cell disease (SCD) is an autosomal recessive disorder characterized by the presence of an abnormal form of Hb (Hb S) within the erythrocytes. This irregular form of Hb is the result of a single mutation in the β-Hb chain where the amino acid glutamic acid at position 6 is substituted with valine.*

The presence of Hb S can cause RBCs to change from their usual biconcave disk shape to a crescent or sickle shape once the oxygen is released (deoxygenated). SCD

occurs when two sickle cell genes are inherited (one from each parent) or one sickle cell gene and another abnormal Hb is inherited, so that almost all of the Hb is abnormal.

Homozygous Hb S occurs when an individual inherits two sickle cell genes. *Heterozygous Hb SC* is the result of inheriting one sickle cell gene and one gene for another abnormal type of Hb called C. Persons with this type of abnormality have fewer complications than those with homozygous Hb S, but they exhibit more ophthalmologic and orthopedic complications.

Heterozygous Hb S β-thalassemia is the result of inheriting one sickle cell gene and one gene for a type of thalassemia, another inherited anemia. Beta thalassemias are caused by genetic mutations that abolish or reduce production of the beta globin subunit of Hb.¹⁴⁵

The sickle cell trait refers to people who carry only one *Hg S* gene and is discussed at the end of this section. Hb F, or fetal Hb, is found in infants. While most infants switch to making α- and β-Hb, some continue to make Hb F, termed hereditary persistence of fetal Hb. For those people who inherit one sickle gene and the hereditary persistence of fetal Hb abnormalities, they make α₂γ₂ Hb and do not develop the severe symptoms of SCD.

Approximately three out of every 1000 black newborns and between 50,000 and 70,000 individuals in the United States have a sickle cell syndrome; the number in Africa is correspondingly higher.¹²⁵ It is a worldwide health problem, affecting many races, countries, and ethnic groups, and is the most common inherited hematologic disorder. The WHO estimates that each year more than 300,000 babies are born worldwide with this inherited blood disorder.²⁰¹

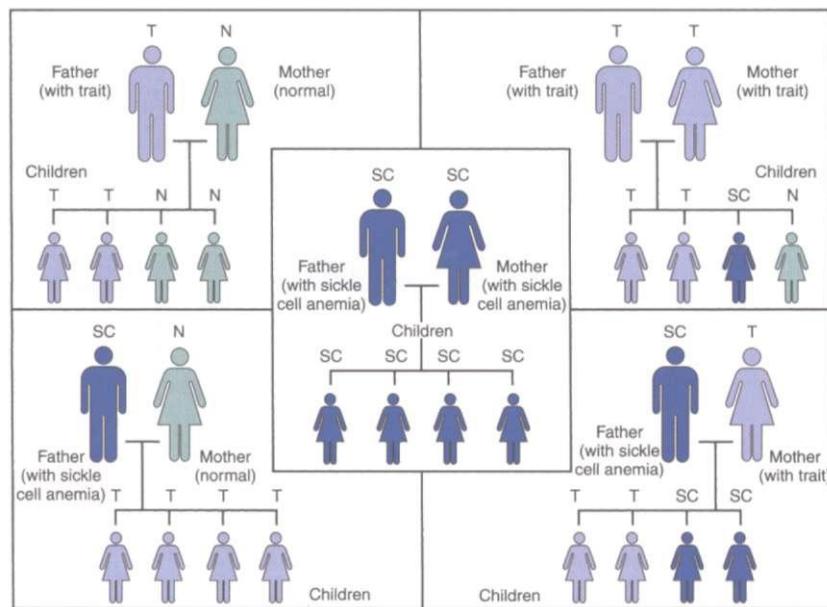
About one in 400 African American newborns in the United States has sickle cell anemia, and one in 12 African Americans (8%) carries the sickle cell trait.¹⁹⁸ The disease is particularly common among people whose ancestors come from sub-Saharan Africa, India, Saudi Arabia, and Mediterranean countries.²⁰¹

The two primary pathophysiologic features of sickle cell disorders are chronic hemolytic anemia and vaso-occlusion resulting in ischemic injury. Children with SCD are at increased risk for severe morbidity and mortality, especially during the first 3 years of life.

When a sickled cell reoxygenates the cell resumes a normal shape, but after repeated cycles of sickling and unsickling the erythrocyte is permanently damaged and hemolyzes. This hemolysis is responsible for the anemia that is a hallmark of SCD. A brief discussion of the related sickle cell syndromes is presented, but only the most severe disorder, sickle cell anemia, is fully discussed in this text.

Etiologic Factors. The cause of SCD and its worldwide incidence is the result of several factors. The sickle cell trait may have developed as a single genetic mutation that provided a selective advantage against severe forms of falciparum malaria.

Anyone who carries the inherited trait for SCD but does not have the actual illness is protected against this form of malaria. In countries with malaria, children born with sickle cell trait survived and then passed the gene for SCD to their offspring. As populations migrated

**Figure 14-14**

Statistical probabilities of inheriting sickle cell anemia. (Reprinted from O'Toole MT: *Miller-Keane encyclopedia and dictionary of medicine, nursing, and allied health*, rev ed, Philadelphia, 2005, Saunders.)

(including the slave trade), the sickle cell trait and sickle cell anemia moved throughout the world.

Several theories purport to explain the origination of SCD, but its actual origin is unknown. Four separate haplotypes are known; each is related to the severity of illness and each is associated with a different geographic location, including different locations in Africa, eastern Saudi Arabia, and India.

Risk Factors. Because SCD is inherited as an autosomal recessive trait, both parents of an offspring must have the sickle Hb gene. When both parents have sickle cell trait, they have a 25% chance with each pregnancy of having a child with sickle cell anemia. If one parent has sickle cell trait and the other has a β -thalassemic disorder, they are at the same risk for having a child with a sickle β -thalassemia syndrome.

In couples in which one individual has sickle cell trait and one has Hb C trait, the chance of having a child with Hb SC disease is also 25% with each pregnancy. If one parent has sickle cell anemia and the other has the sickle cell trait, the risk of having a child with sickle cell anemia is 50% (Fig. 14-14).

Individuals with sickle cell trait can receive nondirective genetic counseling (given objective information without personal bias and without provision of specific recommendations) after Hb electrophoresis and other measurements have been performed on each prospective parent.

Risk factors likely to induce symptoms or episodes (episode is now the preferred term over crisis; however, clinicians may find that some affected individuals prefer the term crisis) are factors that cause physiologic stress, resulting in sickling of the erythrocytes. Stress from viral or bacterial infection, hypoxia, dehydration, extreme temperatures (hot or cold), alcohol consumption, or fatigue may precipitate an episode.

Additionally, episodes may be precipitated by the presence of acidosis; exposure to low oxygen tensions as a result of strenuous physical exertion, climbing to high

altitudes, flying in nonpressurized planes, or undergoing anesthesia without receiving adequate oxygenation; pregnancy; trauma; and fever. Any of these factors may increase the body's need for oxygen, increasing the percentage of erythrocytes that deoxygenate, thereby precipitating an episode.

Pathogenesis. The sickle cell defect occurs in Hb, the oxygen-carrying constituent of erythrocytes. Hb contains four chains of amino acids, the compounds that make up proteins. Two of the amino acid chains are known as *α-globin chains*, and two are called *β-globin chains*.

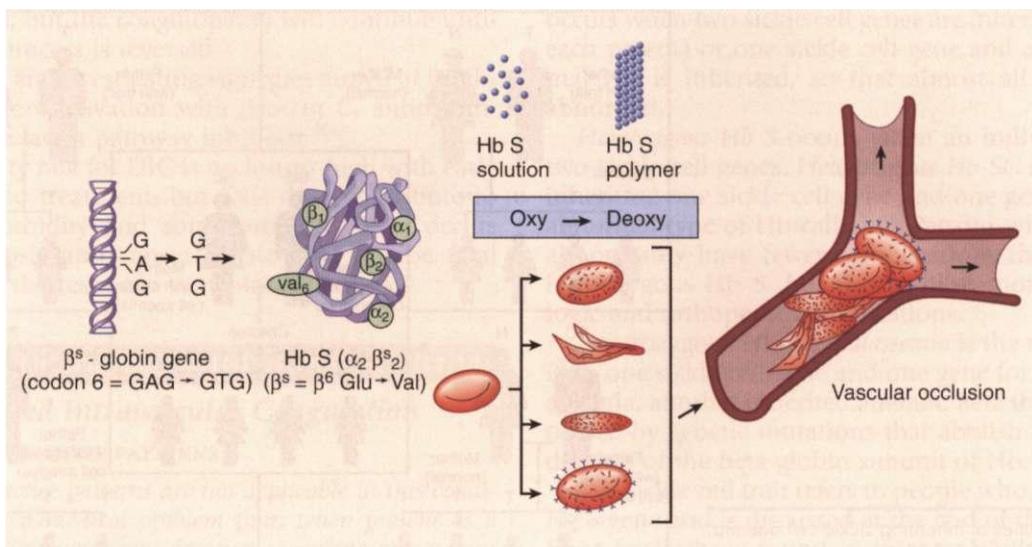
In normal Hb, the amino acid in the sixth position on the β -globin chains is glutamic acid. In people with SCD, the sixth position is occupied by another amino acid, valine (Fig. 14-15). DNA recombinant technology has identified the genetic locus for the β -globin on chromosome 11.

This single-point mutation of valine for glutamic acid results in a loss of two negative charges that causes surface abnormalities. The sickle Hb transports oxygen normally, but after releasing oxygen Hb molecules that contain the β -globin chain defect stick to one another instead of remaining separate and polymerize (change molecular arrangement), forming long, rigid rods or tubules inside RBCs.

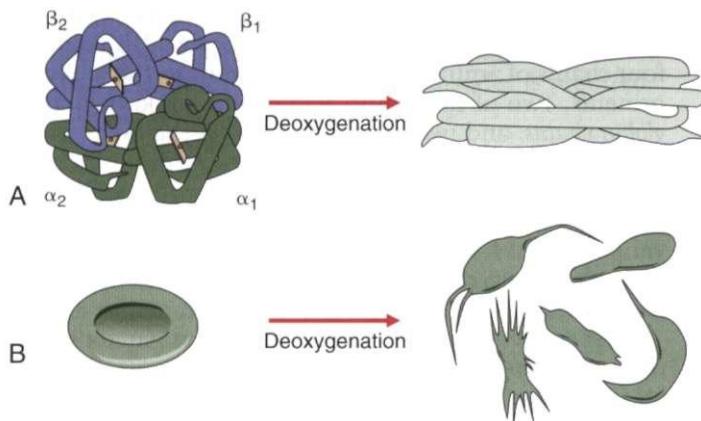
The higher the concentration of deoxygenated sickle Hb molecules and the lower the blood pH, the faster the polymerization occurs.¹⁵⁰ The rods cause the normally smooth, doughnut-shaped RBCs to take on a sickle or curved shape and to lose their vital ability to deform and squeeze through tiny blood vessels (Fig. 14-16).

For a time, this sickling is reversible because the cells are reoxygenated in the lungs; however, eventually the change becomes irreversible. In the process of sickling and unsickling, the erythrocyte membrane becomes damaged and the cells are removed (hemolyzed).

The sickled cells, which become stiff and sticky, clog small blood vessels, depriving tissue from receiving an adequate blood supply. Under stress, tissues experience

**Figure 14-15**

Schematic view of the pathophysiologic characteristics of SCD. The double-stranded DNA molecule on the left represents a β -globin gene in which a $\text{GAG} \rightarrow \text{GTG}$ substitution in the sixth codon has created the sickle cell gene. Valine is substituted for glutamic acid as the sixth amino acid, creating a mutant Hb tetramer (Hb S). A tetramer is a protein with four subunits (tetrameric). Hb S loses solubility and polymerizes when deprived of oxygen. Upon deoxygenation, most sickle cells lose deformability. Some cells sickle; a fraction becomes dehydrated, irreversibly sickled, and poorly deformable; a few become highly adherent. Vaso-occlusion (right) is initiated by adherent cells sticking to the vascular endothelium, thereby creating a nidus that traps rigid cells and facilitates linking together in a chain formation, a process called polymerization. (Reprinted from Goldman L: *Cecil textbook of medicine*, ed 22, Philadelphia, 2004, WB Saunders.)

**Figure 14-16**

A, The molecular structure of Hb contains a pair of α polypeptide chains and a pair of β chains, each wrapped around a heme group (an iron atom in a porphyrin ring). The quaternary structure of the Hb molecule enables it to carry up to four molecules of oxygen. In the folded β -globin chain molecule, the sixth position contacts the α -globin chain. The amino acid substitution at the sixth position of the β -globin chain occurring in sickle cell anemia causes the Hb to aggregate into long chains, altering the shape of the cell (Hb S). **B,** The change of the RBC from a biconcave disk to an elongated or crescent (sickle) shape occurs with deoxygenation.

increased oxygen requirements, which causes more Hb to release its oxygen, leading to increased numbers of deoxygenated and polymerized cells.

Deoxygenation of sickle cells induces potassium (followed by water) efflux, which increases cell density and the tendency of Hb S to polymerize. The sickle cell also has a chemical on the cell surface that binds to blood vessel walls, leading to endothelial cell activation. As a result, these sickle-shaped, rigid, sticky blood cells cannot pass through the capillaries, blocking the flow of blood.¹⁴⁵

Occlusion of the microcirculation increases hypoxia, which causes more erythrocytes to sickle; thus a vicious cycle is precipitated. This accumulation of sickled erythrocytes obstructing blood vessels produces tissue injury. The organs at greatest risk are those with sluggish circula-

tion, low pH, and a high level of oxygen extraction (spleen and bone marrow) or those with a limited terminal arterial supply (eye, head of the femur). No tissue or organ is spared from this injury. The higher the concentration of deoxygenated cells, the more severe (clinically) the complications.

Average sickle RBCs last only 10 to 20 days (normal is 120 days). The RBCs cannot be replaced fast enough, and anemia is the result. Although significant injury occurs in the microvasculature as a result of sickling, the most severe complication of SCD is a cerebral infarct, which occurs in the large blood vessels, where blood is moving rapidly and the diameter is wide.

Research has shown that not only are the Hb cells abnormal, but so are the blood vessel walls. This is likely a product of sickle cells adhering to and damaging

endothelium, which leads to an inflammatory response of WBCs, cytokines, chemoattractants, and procoagulants. Over time, smooth muscle cells migrate into the wall, where they proliferate and narrow the lumen of the vessel.¹⁴⁹

Significantly narrowed or stenotic arteries can further collect sickled cells, thereby occluding the lumen, resulting in stroke. Further complicating stroke and pulmonary hypertension is the lack of nitric oxide production. Normally, when hypoxia is present, nitric oxide is produced to cause local vasodilatation, inhibit endothelial damage, and prevent proliferation of vascular smooth muscle.¹⁸⁹ But the hemolysis of erythrocytes and release of Hb inhibits the production of nitric oxide, thus blocking the beneficial effects of nitric oxide.

Clinical Manifestations. Sickled erythrocytes cause hemolytic anemia and tend to occlude the microvasculature, resulting in both acute and chronic tissue injury. Intravascular sickling and hemolysis can begin by 6 to 8 weeks of age, but clinical manifestations do not usually appear until the infant is at least 6 months old, at which time the postnatal decrease in Hb F, which inhibits sickling, and increased production of Hb S lead to the increased concentration of Hb S.

Acute clinical manifestations of sickling, called *crises* or *episodes*, usually fall into one of four categories: vaso-occlusive or thrombotic, aplastic, sequestration or, rarely, hyperhemolytic (Fig. 14-17).

Pain caused by the blockage of sickled RBCs (thrombosis) is the most common symptom of SCD, occurring unpredictably in any organ, bone, or joint of the body, wherever and whenever a blood clot develops. The symptoms and frequency, duration, and intensity of the painful episodes vary widely (Box 14-9). Some people experience painful episodes only once a year; others may have as many as 15 to 20 episodes annually. The vaso-occlusive episodes causing ischemic tissue damage may last 5 or 6 days, requiring hospitalization and subsiding gradually. Older clients more often report extremity and back pain during vascular episodes.

Chest Syndrome. Two life-threatening thrombotic complications associated with SCD include acute chest syndrome and stroke. Acute chest syndrome results from the inability of sickled cells to become reoxygenated in the lungs. Sickled cells then adhere to lung endothelium cells, resulting in further inflammation, and occlude vessels, causing infarction. The most common precipitants are infection and fat emboli (from infarcted bone marrow).

Symptoms include chest pain, shortness of breath, fever, wheezing, and cough (Box 14-10). Chest radiographs typically demonstrate an infiltrate, sometimes days after the symptoms began. Prognosis for this complication is poor and is one of the most common causes of death.¹⁵⁰

Pulmonary hypertension can be a severe consequence of repeated micro-thrombotic events in the lung even without a history of acute chest syndrome. Autopsy studies suggest that over one third of people with SCD develop this complication (although the real incidence is probably higher). This can develop in clients who have not had a significant number of acute chest syndrome

Box 14-9

CLINICAL MANIFESTATIONS OF SICKLE CELL ANEMIA

Pain

- Abdominal
- Chest
- Headache

Bone and Joint Episodes

- Low-grade fever
- Extremity pain
- Back pain
- Periosteal pain
- Joint pain, especially shoulder and hip

Vascular Complications

- Cerebrovascular accidents
- Chronic leg ulcers
- Avascular necrosis of the femoral head
- Bone infarcts

Pulmonary Episodes

- Hypoxia
- Chest pain
- Dyspnea
- Tachypnea

Neurologic Manifestations

- Seizures
- Hemiplegia
- Dizziness
- Drowsiness
- Coma
- Stiff neck
- Paresthesias
- Cranial nerve palsies
- Blindness
- Nystagmus
- Transient ischemic attacks

Hand-Foot Syndrome

- Fever
- Pain
- Dactylitis

Splenic Sequestration Episodes

- Liver and spleen enlargement, tenderness
- Hypovolemia

Renal Complications

- Enuresis
- Nocturia
- Hematuria
- Pyelonephritis
- Renal papillary necrosis
- End-stage renal failure (older adult population)

Modified from Goodman CC, Snyder TE: *Differential diagnosis for physical therapists: Screening for referral*, ed 4, Philadelphia, 2007, Saunders.

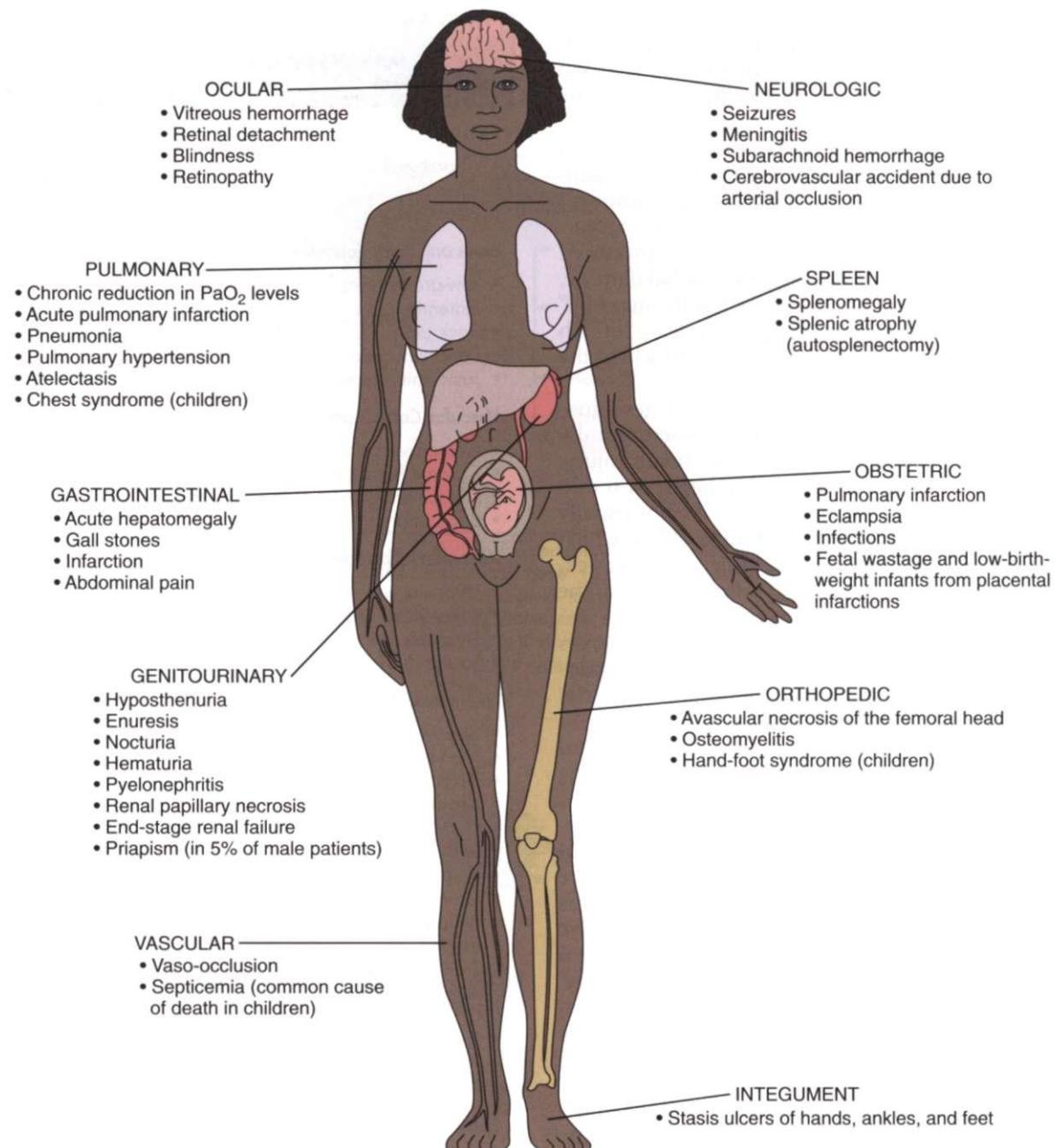


Figure 14-17

Clinical manifestations and possible complications associated with SCD. These findings are a consequence of infarctions, anemia, hemolysis, and recurrent infections.

crises because of the continual microthrombosis that may not be clinically evident.

Eventually, these small vessels become thickened and blocked by thrombin and fibrous tissue with the loss of the vascular bed. This process often proceeds without clinical symptoms until the person is short of breath, at which time the damage is irreversible.

Currently the most sensitive method of detecting pulmonary hypertension early is echocardiography. Pulmonary hypertension increases the risk of sudden death and is a common cause of death in people with SCD.

Stroke. Stroke, or cerebral infarction, is another serious thrombotic complication of SCD. Stroke occurs in 11% of SCD clients under the age of 20 years, causing death or severe disability. Large vessels can become stenotic through chronic injury to the endothelium. Once the diameter of an affected artery is significantly narrowed, acute occluding of the vessel can occur (by a clot made of sickle and normal cells, WBCs, platelets, and thrombin), causing a cerebral infarct.¹⁴⁹

Local production of nitric oxide is typically stimulated by hypoxia to cause a beneficial vasodilatation; but free

Box 14-10**COMPPLICATIONS ASSOCIATED WITH PEDIATRIC SICKLE CELL ANEMIA****Chest Syndrome**

- Severe chest pain
- Fever of $\geq 38.8^{\circ}\text{ C}$ ($\geq 102^{\circ}\text{ F}$)
- Very congested
- Cough
- Dyspnea
- Tachypnea
- Sternal or costal retractions
- Wheezing

Stroke

- Seizures
- Unusual or strange behavior
- Inability to move an arm and/or a leg
- Ataxia or unsteady gait (do not assume these are guarding responses to pain)
- Stutter or slurred speech
- Distal muscular weakness in the hands, feet, or legs
- Changes in vision
- Severe, unrelieved headaches
- Severe vomiting

Hb (from sickle cells breaking apart) inhibits nitric oxide production, resulting in no valuable vasodilatation and further complicating strokes.

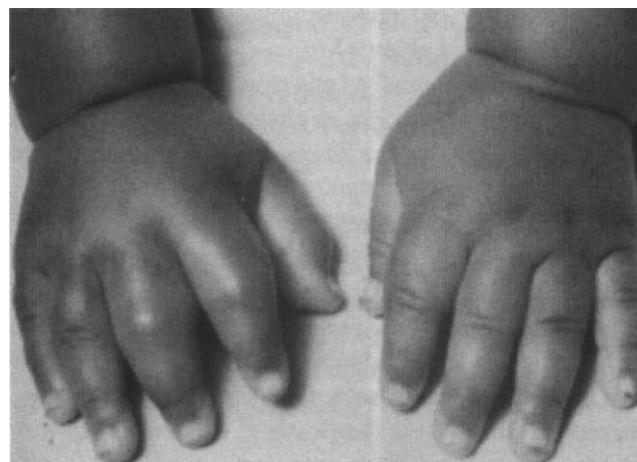
Symptoms are similar to strokes in people without SCD, including paralysis, weakness, speech difficulties, seizures, and tingling/numbness of extremities. Infarcts can occur in the microvasculature as well. MRI and magnetic resonance angiography of the head and neck may show more extensive changes than are seen clinically, suggesting that silent strokes are not uncommon.

Additionally, many cognitive effects from these microvasculature strokes result in learning problems. Children demonstrate problems with memory, attention, visual-motor performance, and academic or social skills; neuromotor delays; mild hearing loss and auditory processing disorders; and failed speech and language screening.^{4,82,101,178}

Other Complications. For most people with SCD, the incidence of complications can be reduced by simple protective measures such as prophylactic administration of penicillin in childhood, avoidance of excessive heat or cold and dehydration, and contact as early as possible with a specialist center. These precautions are most effective if susceptible infants are identified at birth.

Other thrombotic complications include *hand-and-foot syndrome* (dactylitis), which occurs when a microinfarction (clot) occludes the blood vessels that supply the metacarpal and metatarsal bones, causing ischemia; it may be an infant's first problem caused by SCD.

It presents with low-grade fever and symmetric, painful, diffuse, nonpitting edema in the hands and feet, extending to the fingers and toes (Fig. 14-18). This is a fairly common phenomenon seen almost exclusively in the young infant and child. Despite radiographic changes and swelling, the syndrome is almost always self-limiting,

**Figure 14-18**

Dactylitis. Painful swelling of the hands or feet can occur when a clot forms in the hands or feet. This problem, known as hand-and-foot syndrome, occurs most often in children affected by SCD. (Reprinted from Gaston M: *Sickle cell anemia*, NIH Pub No 90-3058, Bethesda, MD, 1990, National Institutes of Health.)

and bones usually heal without permanent deformity (Fig. 14-19).

Priapism is also a thrombotic complication and requires immediate medical attention. The kidneys exhibit thrombotic complications and slowly lose function; end-stage renal disease can occur.

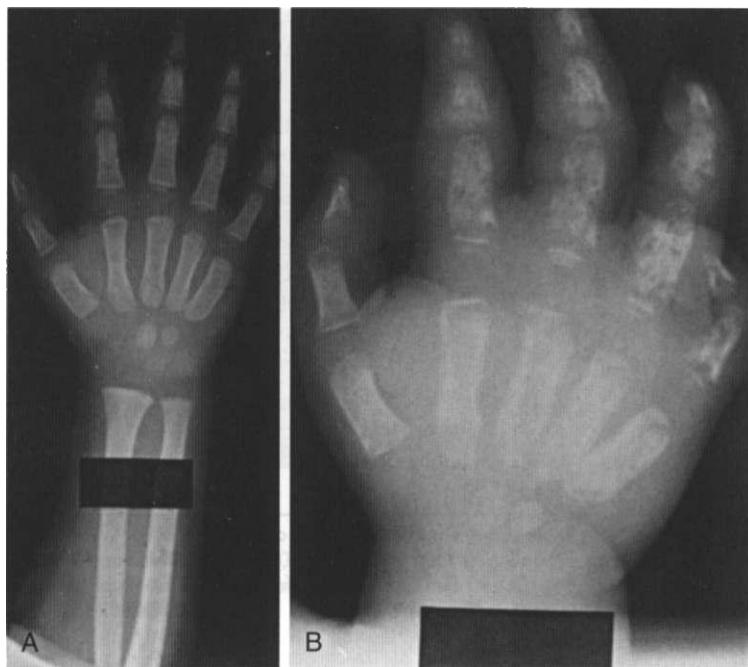
Jaundice is another common manifestation of SCD. Sickled cells do not live as long as normal cells and therefore die more rapidly than the liver can filter them. Bilirubin from these broken down cells builds up in the system, causing jaundice.

Anemia is a constant feature of SCD, with a Hb concentration of around 8 g/dl; acute, severe anemia, termed an aplastic crisis or episode, can occur when erythropoiesis abruptly stops. Clinical manifestations are pallor, fatigue, jaundice, and irritability. This is typically a result of parvovirus B19 infection but is self-limiting in persons with a normal immune system.

Folate deficiency is another cause of severe anemia (often because of noncompliance in taking folate supplements). The typical anemia associated with SCD, because of regular hemolysis, can also lead to jaundice and the formation of gallstones. Anemia can also be worsened by renal insufficiency (decreased levels of erythropoietin) created by thrombosis.

Many of the complications associated with SCD are treated with transfusions, frequently resulting in iron overload. *Hyperhemolysis* develops in some clients due to the formation of alloimmune responses to erythrocyte antigens, resulting in a delayed transfusion reaction with significant acute hemolysis of erythrocytes.

The spleen is an organ that is very susceptible to thrombotic occlusions (i.e., low blood flow, low oxygen tension, and low pH). In sequestration episodes, large numbers of cells undergo sickling in the spleen, leading to ischemia, acute hemolysis, and necrosis of the spleen.

**Figure 14-19**

Radiographs of an infant with sickle cell anemia and acute dactylitis. **A**, The bones appear normal at the onset of the episode. **B**, Destructive changes and periosteal reaction are evident 2 weeks later. (Reprinted from Behrman RE: *Nelson textbook of pediatrics*, ed 17, Philadelphia, 2004, Saunders.)

Hypovolemic shock can occur, particularly in children, accompanied by a tender spleen and splenomegaly. Sequestration episodes may be precipitated by infection and can be fatal in the pediatric population. Over time the spleen is severely damaged and becomes completely fibrotic, called *autosplenectomy*.

The spleen is destroyed in most children with SCD. In children, sickle-shaped RBCs often become trapped in the spleen, leading to a serious risk of death before the age of 7 years from a sudden, profound anemia associated with rapid splenic enlargement or because lack of splenic function permits an overwhelming infection.

Sequestration can occur in the liver but less frequently than splenic sequestration. Children with severe manifestations of sickle cell anemia have low bone mineral density and possess significant deficits in dietary calcium and circulating vitamin D, which complicates growth. Most children have growth retardation by the age of 2 years (weight more than height), which leads to osteoporosis and other bone abnormalities.¹⁰⁶

MEDICAL MANAGEMENT

PREVENTION. Sickling cell anemia can be prevented. Couples at risk of having affected children can be identified by inexpensive and reliable blood tests; chorionic villus sampling from 9 weeks of gestation can be performed for prenatal diagnosis.

Adoption of such measures goes hand in hand with health education. However, prenatal diagnosis can raise ethical questions that differ from one culture to another. Experience has clearly shown that genetic counseling, coupled with the offer of prenatal diagnosis, can lead to a large-scale reduction in births of affected children.

The risk of having affected children can be detected before marriage or pregnancy; however, to do so requires

a carrier screening program. There is extensive experience with such programs in low- and high-income countries. For example, in the case of thalassemia prevention, unmarried people in Montreal (Canada) and the Maldives are offered screening. Premarital screening is a national policy in Cyprus and the Islamic Republic of Iran, and prereproductive screening is emphasized in Greece and Italy.

The WHO recommends these approaches be practiced in conformity with the three core principles of medical genetics: the autonomy of the individual or the couple, their right to adequate and complete information, and the highest standards of confidentiality.²⁰¹

DIAGNOSIS. It is required in every state that all infants be screened for SCD regardless of race or ethnic background (universal screening). This recommendation is based on several factors: (1) one out of every 200 Hispanic and 400 white children in Texas carries the sickle cell trait; (2) although SCD is more prevalent in certain racial and ethnic groups, it is not possible to define accurately an individual's heritage by physical appearance or surname; and (3) prophylactic penicillin and pneumococcal vaccination reduce both morbidity and mortality from pneumococcal infections in infants with sickle cell anemia and sickle thalassemia.

Screening targeted to specific racial and ethnic groups will therefore miss some affected infants, subjecting them to an increased risk of early mortality. Universal screening is the best, most reliable, and most cost-effective screening method to identify affected infants.¹⁴³ The cord blood of newborns is tested in the United States.

The diagnosis of sickle cell trait or any of the other sickle syndromes depends on the demonstration of sickling under reduced oxygen tension. A sickle turbidity test (Sickledex, Streck, Inc., Omaha, NE) can confirm the

presence of Hb S in peripheral blood, and Hb electrophoresis (separation and identification of Hb under the influence of an applied electric field) is used to determine the amount of Hb S in erythrocytes.

Electrophoresis is used to screen blood for sickle cell trait and will also detect SCD and heterozygosity (carrier state) for other Hb disorders, such as Hb C. Because the Hb S and Hb C amino acid substitutions change the electrical charge of the protein, the migration patterns of the Hb with electrophoresis result in distinct diagnostic patterns.¹⁴⁵

Safe, accurate methods for performing prenatal diagnosis for SCD are possible as early as the tenth gestational week. Analyses of DNA from fetal cells obtained by amniocentesis or chorionic villus sampling can be performed at the sixteenth gestational week. The sickle and Hb C genes can be detected directly in fetal DNA samples, as can most Hb S β-thalassemia genes.

TREATMENT. In the past decade, impressive progress has been made in directing treatment to the unique pathophysiology of SCD. A large number of antisickling regimens are being investigated. Although some have been shown to be effective in vitro, unacceptable toxicity prevents their use in human beings at this time.

BMT cures SCD, but minimal availability and associated risks prevent its widespread use. In selected cases BMT may be considered, and the data confirm that allogeneic BMT establishes normal erythropoiesis and is associated with improved growth and stable CNS imaging and pulmonary function in most recipients.^{193,94} The event-free survival rate after allogeneic-matched sibling hematopoietic cell transplant for SCD is 82% at an experienced center.^{13,84}

Supportive care is essential (e.g., rest, pain medication, oxygen, administration of intravenous fluids, electrolytes, and antibiotics, and physical and occupational therapy for joint and bone involvement). Preventive measures (see risk factors above) are used to reduce the incidence of episodes.

Acute stroke is managed with exchange transfusions (i.e., transfusion with erythrocytes and removal of blood) to reduce the amount of Hb S to less than 30% while keeping the total Hb (through transfusions) at 10 g/dL.

The likelihood of a second stroke is increased, and prophylactic transfusions (this inhibits their own erythropoiesis of Hb S) have been shown to help decrease the risk of stroke and reduce the stenosis of arteries.³ Complications with iron overload are common and can have significant long-term problems. Chelating therapy is available but is often difficult for children to tolerate.

Acute chest syndrome is treated with transfusions; oxygen, antibiotics, and hydration may also be needed. Optimal treatment for pulmonary hypertension requires more research. Once the early stages of pulmonary hypertension have been identified, treatments such as hydroxyurea, vasodilators, anticoagulation, oxygen inhalation, and experimental agents such as arginine or nitric oxide can be utilized.

Acute aplastic episodes can be treated with a transfusion if the anemia is severe and the reticulocyte count is low. Most often this is self-limiting and erythropoiesis

resumes in a few days. Splenic or hepatic sequestration requires aggressive rehydration and transfusion.

Exchange transfusions to reduce Hb S levels below 30% of total Hb may be used therapeutically for neurologic, cardiac, or retinal symptoms; hypoxemia; severe prolonged or infarctive episodes; acute splenic sequestration in infants; and chronic leg ulcers. These transfusions also can be used prophylactically during pregnancy or before general anesthesia, but they carry the risk of hepatitis, RBC sensitization, hemosiderosis (increased iron storage), and transfusion reactions.

Hydroxyurea is a medication that stimulates Hb F production and is used as a treatment for sickle cell anemia. It is considered safe in the pediatric population. Dramatic reduction of painful episodes, fewer hospitalizations, decreased need for transfusions, and fewer cases of acute chest syndrome occur with the use of hydroxyurea.¹⁷⁹ Neutropenia is a potential side effect requiring frequent monitoring.¹⁰⁰ Erythropoietin may be useful to increase erythropoiesis in clients with renal disease.

Vaccinations are vital, particularly an annual influenza vaccine and a pneumococcal vaccine every 5 years.

Prenatal and neonatal screening can identify this disorder and significantly reduce morbidity and mortality through the use of prophylactic antibiotics. Infants with documented SCD (sickle cell anemia or Hb S (3-thalassemia) should be started on twice-daily oral prophylactic penicillin as soon as possible but no later than 2 months of age. Children who have experienced pneumococcal sepsis should remain on prophylactic penicillin indefinitely.

The use of inhaled nitrous oxide to treat SCD is also under investigation because of its ability to prevent pulmonary hypertension and endothelial damage. The onset of peripheral neuropathy associated with nitric oxide use in this population has delayed the final development of treatment protocols incorporating nitric oxide.^{138,183}

Researchers are continuing to investigate the use of fetal Hb as a treatment possibility. Fetal Hb is produced during fetal development and for the first 6 months after birth. Hb F has some ability to prevent sickling and reduce hemolysis; some adults with SCD who naturally make substantial amounts of Hb F have less pain and better spleen function than others with SCD who do not have elevated levels of Hb F.

Other researchers are investigating drugs to reverse cellular dehydration (dehydration increases the rate of polymerization) and fetal cord blood transplantation (see Chapter 21). *Stem cell transplantation* has been shown to help, and possibly cure, individuals with SCD.⁸⁸

Stem cells taken from a brother or sister may provide bone marrow that is a perfect match (same tissue type) for the recipient. Unfortunately, only about 10% to 20% of children with sickle cell have a matched sibling donor. Stem cells from partially matched (partial tissue match) family members have been tried with a few children who have SCD.⁸⁸

The risk and benefits of these types of transplants are not as well known as transplants using a matched donor. When children with SCD have no matched brother or sister donor, allogeneic transplants are a possible treatment available for these patients.

PROGNOSIS. Historically, SCD has been associated with high mortality in early childhood due to overwhelming bacterial infections, acute chest syndrome, and stroke. In the mid-1970s the average life expectancy was only 14.3 years. By 1994 the life expectancy had increased to 42 years for men and 48 years for women with sickle cell anemia.^{151,201} This increase is attributed to better general medical treatment.

SCD remains a devastating condition with recurrent episodes leading to early death. The complications of SCD can be life threatening depending on their location. Recovery may be complete in some cases, but serious neurologic damage is more likely to occur, and repeated cerebrovascular accidents may lead to increased neurologic involvement, permanent paralysis, or death. Permanent damage from blood clots to the heart, kidney, lungs, liver, or eyes (blindness) can occur.

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-15

Sickle Cell Disease

PREFERRED PRACTICE PATTERNS

4B: Impaired Posture (brain, impaired joint mobility, leg length discrepancy, muscle imbalance, muscle weakness)

4E: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Localized Inflammation (joint effusion)

4G: Impaired Joint Mobility, Muscle Performance, and Range of Motion Associated with Fracture (aseptic necrosis, stress fracture)

5B: Impaired Neuromotor Development

6A: Primary Prevention/Risk Reduction for Cardiovascular/Pulmonary Disorders (emboli; stroke prevention)

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

6F: Impaired Ventilation and Respiration/Gas Exchange Associated with Respiratory Failure (pulmonary infarct, pneumonia, acute chest syndrome)

7A: Primary Prevention/Risk Reduction for Integumentary Disorders (chronic leg ulcers)

7B: Impaired Integumentary Integrity Associated with Superficial Skin Involvement (ulcers; possibly pattern 7C)

It is important for the therapist to recognize signs of complications, especially signs of acute chest syndrome, stroke, and neurodevelopmental impairment (see Box 14-10). Providing client education is also an important role. Clients should be taught about risks and risk prevention, including the importance of physical activity and/or mobility, prevention of pulmonary complications using breathing and incentive spirometry, and the importance of remaining well hydrated. Screening for referral to other rehabilitation or behavioral services is also part of the therapist's intervention.

Stroke is a relatively infrequent complication in the young infant; the median age for occurrence of stroke in children is 7 years. Splenic sequestration (entrapment of blood and enlargement in the spleen) can

occur in children younger than 6 years with homozygous Hb S and at any age with other types of SCD. Circulatory collapse and death can occur in less than 30 minutes.

Any signs of weakness, abdominal pain, fatigue, dyspnea, tachycardia accompanied by pallor, and hypotension require emergency medical attention. Client and family education should emphasize the importance of regularly scheduled medical evaluations for anyone receiving hydroxyurea. The risk of developing an undetected toxicity that can result in severe bone marrow depression must be explained. Outward signs of drug complications are rarely evident.

Neurodevelopment

SCD is a blood disorder; however, the CNS is one of the organs frequently affected by the disease.^{81,167} Brain disease can begin early in life and often leads to neurocognitive dysfunction.

Approximately one fourth to one third of children with SCD have some form of CNS effects from the disease, which typically manifest as deficits in specific cognitive domains and academic difficulties.

The impact of the disease on families shares many features similar to other neurodevelopmental disorders; however, social-environmental factors related to low socioeconomic status, worry and concerns about social stigma, and recurrent, unpredictable medical complications can be sources of relatively higher stress in SCD.

Greater public awareness of the neurocognitive effects of SCD and their impact on child outcomes is a critical step toward improved treatment, adaptation to illness, and quality of life.

Exercise

Multiple factors contribute to exercise intolerance in individuals with sickle cell anemia, but little information exists regarding the safety of maximal cardiopulmonary exercise testing or the mechanisms of exercise limitation in these clients.

For example, low peak Vo_2 , low anaerobic threshold, gas exchange abnormalities, and high ventilatory reserve comprise a pattern consistent with exercise limitation due to pulmonary vascular disease in this population group. Low peak Vo_2 , low anaerobic threshold, no gas exchange abnormalities, and a high heart rate reserve reflect peripheral vascular disease and/or myopathy. Low peak Vo_2 , low anaerobic threshold, no gas exchange abnormalities, and a low heart rate reserve are best explained by anemia.²⁶⁴ These kinds of cardiopulmonary factors must be considered when prescribing exercise for this population.¹³⁹

During a sickle cell episode, the therapist may be involved in nonpharmacologic pain control or management. Precautions include avoiding stressors that can precipitate an episode, such as overexertion, dehydration, smoking, and exposure to cold or the use of cryotherapy for painful, swollen joints. (See Special Implications for the Therapist: Hematologic Disorders in this chapter.)

Should a person with SCD experience an isolated musculoskeletal injury (e.g., sprained ankle) in the absence of any sickle cell episodes, careful application of ice can be undertaken.

Pain Management

People with SCD suffer both physically and psychosocially. They may describe feelings of helplessness against the disease and fear a premature death. Frequent hospitalizations and consequent job absences often result in stressful financial constraints.

Depression is a common finding in this group of people. A program offering holistic treatment focuses on pharmacologic and nonpharmacologic strategies, offering the client multiple self-management options. The sickle cell pain can be successfully managed using whirlpool therapy at a slightly warmer temperature (102° F to 104° F), facilitating muscle relaxation through active movement in the water.

The therapist should teach the client alternative methods of pain control, such as the appropriate application of mild heat to painful areas or the use of visualization or relaxation techniques. Combined use of medications, psychologic support, relaxation techniques, biofeedback, and imagery is a useful intervention to lessen the effects of painful episodes.⁷⁹ Cognitive-behavioral therapy can be helpful in the management of sickle pain because of the high level of psychologic stress people with SCD experience.¹⁸⁷

Joint effusions in SCD can occur secondary to long bone infarctions with extension of swelling and septic arthritis. Clients with SCD may also have coexistent rheumatic or collagen vascular disease or osteoarthritis, necessitating careful evaluation to determine the presence of marked inflammation or fever before initiating intervention procedures.

Teaching joint protection is important and may include assistive devices, equipment, and technology and pain-free strengthening exercises. Persistent thigh, buttock, or groin pain in anyone with known SCD may be an indication of aseptic necrosis of the femoral head. Blood supply to the hip is only adequate, even in healthy people, so the associated microvascular obstruction can leave the hip especially vulnerable to ischemia and necrosis. Up to 50% of sickle cell cases develop this condition.

Total hip replacement may be indicated in cases in which severe structural damage occurs; sickle cell-related surgical complications most commonly include excessive intraoperative blood loss, postoperative hemorrhage, wound abscess, pulmonary complications, and transfusion reactions.¹⁹⁰

Tolerance, Dependence, and Addiction

It is helpful if the client, family, and clinician understand the differences among tolerance, dependence, and addiction as they relate to the individual with SCD receiving or needing narcotic medications. Tolerance and dependence are both involuntary and predictable physiologic changes that develop with repeated administration of narcotics; these terms do not indicate the person is addicted.

Tolerance occurs when, after repeated administration of a narcotic, larger doses are needed to obtain the same effect. *Dependence* has occurred if withdrawal symptoms emerge when the narcotic is stopped abruptly. In either case, this means that once the medication is no longer needed, the dosage will have to be tapered down to avoid withdrawal symptoms.

Addiction, although also based on physiologic changes associated with drug use, has a psychologic and behavioral component characterized by continuous craving for the substance. Addicted people will use a drug to relieve psychologic symptoms even after the physical pain is gone.

The chronic use of narcotics for pain relief may lead to addictive use in vulnerable individuals, but even if someone is addicted, the pain should still be treated and narcotics should not be withheld if they are the drugs of choice for the pain condition. Ironically, undertreating the pain because of fear of fostering addiction actually encourages a pattern of drug-seeking and drug-hoarding behaviors.⁷²

Sickle Cell Trait

Sickle cell trait is not a disease but rather a heterozygous condition in which the individual has the mutant gene from only one parent (β^s gene) and the normal gene (β^A globin gene), resulting in the production of both Hb S and Hb A, with a predominance of Hb A (60%) over Hb S (40%). One in 12 African Americans (8%) has the sickle cell trait, and many other races and nationalities also carry the genetic defect. The gene has persisted because heterozygotes gain slight protection against falciparum malaria.

Under normal circumstances, sickle cell trait is rarely symptomatic; symptoms may occur with conditions associated with marked hypoxia and at high altitudes. No increased risk is evident for individuals with sickle cell trait who undergo general anesthesia, and a normal life expectancy is predicted. It was previously reported that no increased risk of sudden death was evident for those who participate in athletics, but a small number of cases have now been reported.

However, it remains controversial whether the pathogenesis of these exercise-related deaths involved microvascular obstruction by sickled erythrocytes since sickling can occur postmortem. The recommendations are that athletes with sickle cell trait adhere to compliance with general guidelines for fluid replacement and acclimatization to hot conditions and altitude.¹⁷³

The Thalassemias

Definition. The thalassemias are a group of inherited disorders with abnormalities in one or more of the four globin genes. Hb is composed of four protein chains: 2 α -globin chains and 2 β -globin chains (see Fig. 14-16). These four proteins are attached to heme (iron and protoporphyrin), which allows a molecule of oxygen to reversibly bind to this complex molecule.

Depending on which globin chain is affected, people may have α -thalassemia or β -thalassemia. α -Thalassemia is common among people from Africa, the Mediterranean (*thalassa* is Greek for sea, referring to early cases of SCD reported around the Mediterranean), the Middle East, and Asia. β -Thalassemia is most prevalent in the Mediterranean, Southeast Asia, India, and Pakistan.

Overview and Pathogenesis. The thalassemias are characterized by abnormalities in the globin genes leading to incomplete or abnormal formation of Hb. This results in ineffective erythropoiesis and chronic hemolysis. Because there are four α -globin genes, several diseases can occur.

Clients who lack only one gene ($-\alpha/\alpha\alpha$) manifest no clinical symptoms and are carriers of the disorder. If two a genes are deleted ($-, \alpha$ or $-\alpha/-\alpha$), this condition is termed a-thalassemia trait and results in mild anemia. Hb H disease is characterized by three a gene deletions ($-, -\alpha$) and results in severe anemia, CHF, and death. Fetal death occurs when all four of the a genes are deleted (hydrops fetalis).

Whereas α -thalassemia occurs with gene deletions, β -thalassemia is a heterogenous group of disorders caused by various genetic anomalies (usually point mutations), resulting in defects in the production of β -globin chains.

Thalassemia major (also called Cooley's anemia) results from significant genetic defects in both β -globin genes, leading to a lack of β -globin chain synthesis. β -Thalassemia intermedia is caused by a mutation in each of the β -globin genes, with one mutation being mild, allowing for more β -globin chains to be produced with improved function compared with β -thalassemia major.

$^-\alpha$ -Thalassemia trait is characterized by only one gene having a mutation. Normally, the α - and β -globin chains are produced in an even ratio. When thalassemia occurs, there is a mismatch of globin chains produced. In persons affected with severe mutations, there are five to six times the number of normal precursor erythrocytes and 15 times the number of cells in apoptosis (programmed cell death) in the bone marrow as the body attempts to compensate for anemia. The cells that are released from the bone marrow may be rigid and unable to adapt to the size of the small capillaries or cleared by the immune system, resulting in hemolysis.¹⁶⁴

Clinical Manifestations. α -Thalassemia is not as common as β -thalassemia. The clinical manifestations of β -thalassemia vary depending on the severity and number of mutations. The clinical manifestations of thalassemia are primarily attributable to (1) defective synthesis of Hb (ineffective erythropoiesis), (2) structurally impaired RBCs, and (3) hemolysis or destruction of the erythrocytes.

β -Thalassemia major exhibits the most severe complications of the β -thalassemias due to significant genetic mutations. Most of these complications are a result of severe anemia and iron overload (from blood transfusions and increased absorption from the gut).

Clients with β -thalassemia major require frequent and regular transfusions beginning in infancy. Anemia and iron overload lead to endocrinopathies, cardiomyopathy, and cirrhosis of the liver. The endocrinopathies can be

severe, including diabetes mellitus, hypoparathyroidism, hypopituitarism, delayed puberty, testicular and ovarian failure, and hypothyroidism.

These endocrine problems along with the anemia result in bone deformities and osteoporosis (increasing the risk for fractures). As a reaction to the anemia, the body attempts to compensate by making erythrocytes in extra medullary locations, including the spleen and liver (causing hepatosplenomegaly). Because the bone marrow is filled with more cells than normal, there is bone expansion (often noted on the skull).

Multiple and frequent transfusions place the client at risk for all complications related to transfusions, although cardiomyopathy is the most common cause of death.¹⁶⁴ Clients with thalassemia intermedia exhibit mild to moderate anemia. Transfusion requirements are less than that received by clients with thalassemia major, but depending on the severity of the mutations, clients may still develop splenomegaly, iron overload, and bone deformities.

Persons with the thalassemia trait typically have mild or no anemia. Their erythrocytes may be very small, but splenomegaly and bone deformities do not develop.

MEDICAL MANAGEMENT

DIAGNOSIS. Diagnosis is by laboratory testing. The peripheral blood smear may demonstrate target cells (RBCs that appear like a target), fragments of erythrocytes (because of hemolysis), and very small RBCs (see Fig. 14-2). The serum bilirubin and fecal and urinary urobilinogen levels may be elevated due to the severe hemolysis of abnormal cells. Electrophoresis is usually diagnostic for all types of thalassemia except α -thalassemia trait.

TREATMENT. The anemia associated with thalassemia intermedia may range from mild (not requiring transfusions) to more moderate, requiring occasional transfusions. The goal is to maintain an Hb level of 9 to 10 g/dL, which allows for more normal development and growth and reduces the incidence of hepatosplenomegaly and bone deformities. Clients requiring more frequent transfusions can develop clinical manifestations as described above.

Treatment for thalassemia major consists of optimizing transfusions, providing chelation therapy for iron overload, and implementing hormone replacement as needed. Thalassemia major requires lifelong transfusion, which places these persons at risk for transfusion-related infectious diseases.

The blood supply in the United States is rigorously tested, resulting in a significantly decreased incidence of hepatitis B and C and HIV, although transmission of these viruses can still occur. Most blood is also leukodepleted (WBCs removed) to reduce the problems of transfusion reactions and cytomegalovirus transmission.

Chelators remove iron from the bloodstream, and routine use in these clients has led to a doubling of life expectancy.⁸⁰ Deferoxamine is the most common agent given, although intravenous dosing and side effects make its use difficult. Newer oral chelating agents are being developed, including deferasirox. This drug also has

several significant adverse effects, although it does provide the advantages of oral administration and the ability to enter cells and chelate intracellularly.

An experimental approach is to combine the two drugs to provide intracellular chelation along with good plasma chelation. Progressive disease (or in clients who do not respond to chelation therapy) often requires hormone replacement. Clients can receive growth hormone, hormone replacement for testicular and ovarian failure, insulin for diabetes, levothyroxine for hypothyroidism, and calcium and vitamin D (and perhaps bisphosphonates) for osteoporosis.

BMT is an option for clients without severe complications (e.g., liver cirrhosis). Other experimental treatments include agents that increase fetal Hb production, such as 5-azacytidine, butyric acid, and hydroxyurea (see Sickle Cell Anemia: Treatment above), although transfusion decreases the responsiveness of the bone marrow to these agents.

Human recombinant erythropoietin and antioxidants may aid in treatment, but guidelines and study results are still pending. Gene therapy has been successful in animal (mice) studies, but enormous hurdles need to be crossed to be clinically feasible.^{58,120,188}

PROGNOSIS. Thalassemia trait does not affect life expectancy, but clients who carry the mutation need genetic counseling. Until recently the outlook for clients with thalassemia major has been poor, with lethal, severe hemolytic anemia and subsequent iron overload and dysfunction of almost all organ systems.

Children are significantly delayed in growth and development; delay of puberty is universal and many die before puberty. Treatment with blood transfusion and early chelation therapy has improved life expectancy from early puberty to early adulthood. Death from *hydrops fetalis* occurs in homozygous α -thalassemia and consistently results in stillbirth or death in utero.

References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this textbook. The reader can view the reference source and access it on-line whenever possible. There are a total of 208 cited references and other general references for this chapter.

CHAPTER 15

The Respiratory System

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OVERVIEW

Anatomically, the respiratory system can be divided into three main portions: the upper airway, the lower airway, and the terminal alveoli (Fig. 15-1). The upper airway consists of the nasal cavities, sinuses, pharynx, tonsils, and larynx. The lower airway consists of the conducting airways, including the trachea, bronchi, and bronchioles (Fig. 15-2). The alveoli, or air sacs, at the end of the conducting airways in the lower respiratory tract are the primary lobules, sometimes called the *acini*, of the lung.

Physiologically, lung function is comprised of ventilation and respiration. *Ventilation* is the ability to move the air in and out of the lungs via a pressure gradient. *Respiration* is the gas exchange that supplies oxygen to the blood and body tissues and removes carbon dioxide. Pathology or impairment of the airways, lungs, chest wall, and diaphragm will affect ventilation. Pathology of the lungs and cardiovascular system, as well as peripheral tissues, will affect respiration.

Major Sequela of Pulmonary Disease or Injury

Hypoxemia is the most common condition caused by pulmonary disease or injury. *Hypoxemia*, deficient oxygenation of arterial blood, may lead to *hypoxia*, a broad term meaning diminished availability of oxygen to the body tissues. Prolonged hypoxia will cause tissue damage or death. Hypoxemia is caused by respiratory alterations (Table 15-1) or cardiovascular compromise, whereas hypoxia may occur anywhere in the body caused by alterations of other systems and may not be related to changes in the pulmonary system.

Signs and symptoms of hypoxemia vary, depending on the level of oxygenation in the blood (Table 15-2). Exercise testing may be performed to determine the degree of oxygen desaturation and/or hypoxemia that occurs on exertion. This testing requires analysis of arterial blood samples drawn with the subject at rest and at peak exercise. Continuous noninvasive measurement of arterial oxyhemoglobin saturation is usually determined by pulse oximetry.

Oxygen Transport Deficits in Systemic Disease

Although this chapter focuses on primary pulmonary impairment, pathologic conditions of every major organ system can have secondary effects on pulmonary function and on the oxygen transport pathway (which includes the cardiovascular system). Such effects are of considerable clinical significance given that they can be life-threatening and that therapy interventions usually put additional demands on the oxygen transport system. The resulting secondary effect may include a large range of pulmonary impairments such as altered ventilation, perfusion, and ventilation/perfusion matching; reduced lung volumes, capacities, and flow rates; atelectasis; reduced surfactant production and distribution; impaired mucociliary transport; secretion accumulation; pulmonary aspiration; impaired lymphatic drainage; pulmonary edema; impaired coughing; and respiratory muscle weakness or fatigue.¹¹

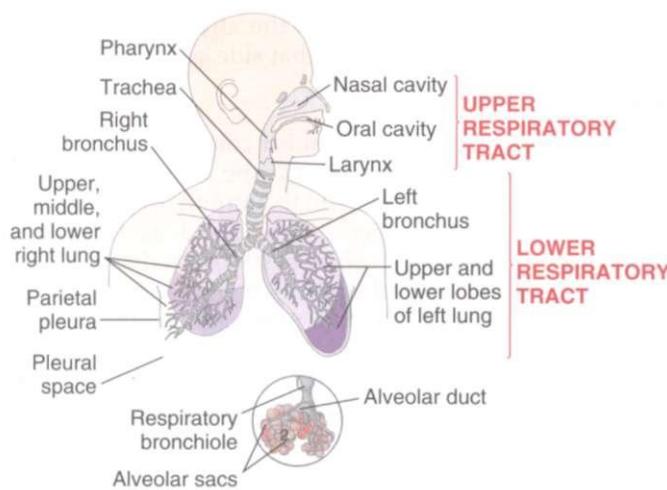
When assessing signs and symptoms of pulmonary disease, the therapist must consider the possibility that these are secondary effects and should investigate the nature of the underlying etiologic factors. Making as specific a physical therapy diagnosis as possible enables the therapist to identify and implement the most effective interventions.

Signs and Symptoms of Pulmonary Disease

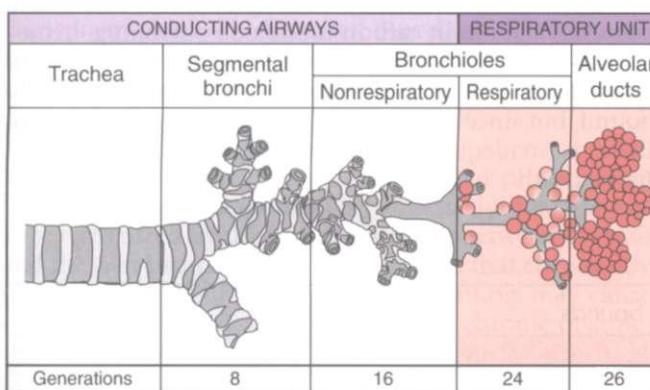
Pulmonary disease is often classified as acute or chronic, obstructive or restrictive, or infectious or noninfectious and is associated with many common signs and symptoms. The most common of these are cough and dyspnea. Other manifestations include chest pain, abnormal sputum, hemoptysis, cyanosis, digital clubbing, and altered breathing patterns (Box 15-1 and Table 15-3).

Cough

As a physiologic response, cough occurs frequently in healthy people, but a persistent dry cough may be caused by a tumor, congestion, or hypersensitive airways (allergies). A productive cough with purulent sputum may

**Figure 15-1**

Structures of the upper and lower respiratory tracts. The upper respiratory tract consists of the nasal cavity, pharynx, and larynx; the lower respiratory tract includes the trachea, bronchi, and lungs. The circle shows the acinus, the terminal respiratory unit, which consists of the respiratory bronchioles, alveolar ducts, and alveolar sacs. This is the portion of the lungs where oxygen and carbon dioxide are exchanged.

**Figure 15-2**

Structures of the lower airway. The first 16 generations of the airways branching in human lungs are purely conducting; transitional airways lead into the final respiratory zone consisting of alveoli where gas exchange takes place.

indicate infection, whereas a productive cough with nonpurulent sputum is nonspecific and indicates airway irritation. Hemoptysis (coughing and spitting blood) indicates a pathologic condition—*infection, inflammation, abscess, tumor, or infarction*.

Dyspnea

Shortness of breath (SOB), or dyspnea, usually indicates hypoxemia but can be associated with emotional states, particularly fear and anxiety. Dyspnea is usually caused by diffuse and extensive rather than focal pulmonary disease, pulmonary embolism being the exception. Factors contributing to the sensation of dyspnea include increased work of breathing (WOB), respiratory muscle fatigue, increased systemic metabolic demands, and decreased respiratory reserve capacity. Dyspnea when the

Table 15-1 Causes of Hypoxemia

Mechanism	Common Clinical Cause
Ventilation/perfusion mismatch	Asthma Chronic bronchitis Pneumonia High altitude Low oxygen content Enclosed breathing space (suffocation)
Decreased oxygen content	Lack of neurologic stimulation of the respiratory center Oversedation Drug overdose Neurologic damage
Hypoventilation	COPD Emphysema Fibrosis Edema ARDS
Alveolocapillary diffusion abnormality	Hyaline membrane disease (ARDS in newborn)
Pulmonary shunting	Atelectasis

Modified from McCance KL, Huether SE, eds: *Pathophysiology: the biologic basis for disease in adults and children*, ed 3, St Louis, 1998, Mosby-Year Book.

COPD, Chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome.

Table 15-2 Signs and Symptoms of Hypoxemia

Pao ₂ (mm Hg)	Signs and Symptoms
80-100	Normal
60-80	Moderate tachycardia, possible onset of respiratory distress, dyspnea on exertion
50-60	Malaise Light-headedness Nausea Vertigo Impaired judgment Incoordination Restlessness
35-50	Marked confusion Cardiac arrhythmias Labored respiration Cardiac arrest
25-35	Decreased renal blood flow Decreased urine output Lactic acidosis Lethargy Loss of consciousness
<25	Decreased minute ventilation* secondary to depression of the respiratory center

Modified from Frownfelter DL, Dean E: *Principles and practice of cardiopulmonary physical therapy*, ed 4, St Louis, 2006, Mosby-Year Book.

Pao₂, Partial pressure of arterial oxygen.

*The total expired volume of air per minute.

person is lying down is called *orthopnea* and is caused by redistribution of body water. Fluid shift leads to increased fluid in the lung, which interferes with gas exchange and leads to orthopnea. In supine and prone, the abdominal contents also exert pressure on the diaphragm, increasing the WOB and often limiting vital capacity.

Chest Pain

Pulmonary pain patterns are usually localized in the substernal or chest region over involved lung fields, including the anterior aspect of the chest, side, or back. However, pulmonary pain can radiate to the neck, upper trapezius, costal margins, thoracic area of the back, scapulae, or shoulder. Shoulder pain caused by pulmonary involvement may radiate along the medial aspect of the arm, mimicking other neuromuscular causes of neck or shoulder pain. Musculoskeletal causes of chest (wall) pain must be differentiated from pain of cardiac, pulmonary, epigastric, and breast origins.

Extensive disease may occur in the lung without occurrence of pain until the process extends to the parietal pleura (Fig. 15-3). Pleural irritation then results in sharp, localized pain that is aggravated by any respiratory movement. Clients usually note that the pain is alleviated by

Box 15-1

MOST COMMON SIGNS AND SYMPTOMS OF PULMONARY DISEASE

- Cough
- Dyspnea
- Abnormal sputum
- Chest pain
- Hemoptysis
- Cyanosis
- Digital clubbing
- Altered breathing patterns

autosplinting, that is, lying on the affected side, which diminishes the movement of that side of the chest.^{375,392}

Cyanosis

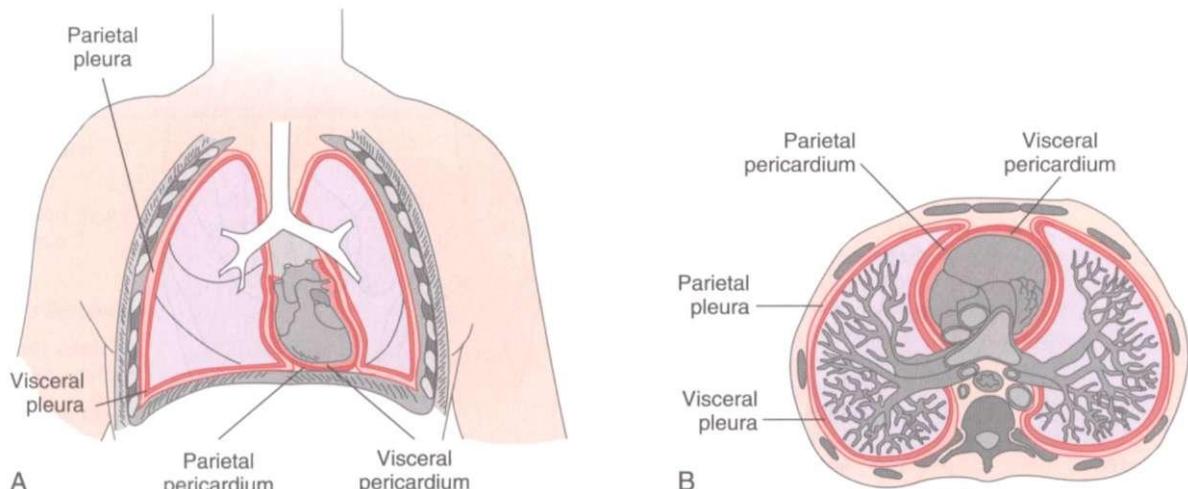
The presence of cyanosis, a bluish color of the skin and mucous membranes, depends on the oxygen saturation of arterial blood and the total amount of circulating hemoglobin. It is further differentiated as central or peripheral. Central cyanosis is best observed as a bluish discoloration in the oral mucous membranes, lips, and conjunctivae (i.e., the warmer, more central areas) and is most often associated with cardiac right-to-left shunts and pulmonary disease. Peripheral cyanosis is associated with decreased perfusion to the extremities, nail beds, and nose (i.e., the cooler, exposed areas) and is commonly caused by cold external temperature, anxiety, heart failure, or shock.

Clinically detectable cyanosis depends not only on oxygen saturation but also on the total amount of circulating hemoglobin that is bound to oxygen. For example, a child with severe anemia may not be cyanotic because all available hemoglobin is fully saturated with oxygen. However, a child with polycythemia may demonstrate signs of cyanosis because the overproduction of red blood cells (RBCs) results in increased amounts of hemoglobin that are not fully saturated with oxygen. In some instances, however, such as in carbon monoxide poisoning, hemoglobin is bound with a substance other than oxygen. Cyanosis is not present since the hemoglobin is fully bound, but since the hemoglobin is not bound to oxygen, there is inadequate tissue oxygenation and potential tissue death.

Table 15-3 Descriptions of Altered Breathing Patterns and Sounds

Breathing Pattern or Sound	Description
Apneustic	Gasping inspiration followed by short expiration.
Biot's respiration (ataxia)	An irregular pattern of deep and shallow breaths; fast, deep breaths interspersed with abrupt pauses in breathing.
Cheyne-Stokes respiration	Repeated cycle of deep breathing followed by shallow breaths or cessation of breathing.
Crackles/rales	Discontinuous, low-pitched sounds predominantly heard during inspiration that indicate secretions in the peripheral airways. ¹⁴⁰
Hyperventilation	Abnormally prolonged and deep breathing.
Hypoventilation	Reduction in the amount of air entering the pulmonary alveoli, which causes an increase in the arterial CO ₂ level.
Kussmaul's respiration	A distressing dyspnea characterized by increased respiratory rate (>20/min), increased depth of respiration, panting, and labored respiration typical of air hunger.
Lateral-costal breathing	Chest becomes flattened anteriorly with excessive flaring of the lower ribs (supine position); minimal to no upper chest expansion or accessory muscle involvement with outward flaring of the lower rib cage instead; the person breathes into the lateral plane of respiration (gravity eliminated) because the weakened diaphragm and intercostal muscles cannot effectively oppose the force of gravity in the anterior plane; used to focus expansion in areas of the chest wall that have decreased expansion (e.g., spinal cord injury with atelectasis or pneumonia, asymmetric chest expansion with scoliosis).*
Paradoxical breathing (sometimes referred to as reverse breathing)	All or part of the chest wall falls in during inspiration; may be abdominal expansion during exhalation; can lead to a flattened anterior chest wall or pectus excavatum.
Stridor	A shrill, harsh sound heard during inspiration in the presence of laryngeal obstruction.
Wheezing	High-pitched, continuous whistling sound, usually with expiration and related to bronchospasm or other constriction of the airways.

*From Massery M: Personal communication, 2001.

**Figure 15-3**

Chest cavity and associated structural linings shown in anterior, **A**, and cross-sectional, **B**, views. For instructional purposes the layers are depicted larger than actually found in the human body.

Arterial saturation in central cyanosis is usually decreased, whereas arterial saturation may be normal in peripheral cyanosis. In the case of peripheral cyanosis, vasoconstriction with decreased blood supply and perfusion rather than unsaturated blood is the underlying cause of symptoms.

Clubbing

Thickening and widening of the terminal phalanges of the fingers and toes result in a painless clublike appearance recognized by the loss of the angle between the nail and the nail bed (Fig. 15-4). Conditions that chronically interfere with tissue perfusion and nutrition may cause clubbing, including cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), lung cancer, bronchiectasis, pulmonary fibrosis, congenital heart disease, and lung abscess. Although 75% to 85% of clubbing is due to pulmonary disease and resultant hypoxia (diminished availability of blood to the body tissues), clubbing does not always indicate lung disease. It is sometimes present in heart disease, peripheral vascular disease, and disorders of the liver and gastrointestinal tract.

Altered Breathing Patterns

Changes in the rate, depth, regularity, and effort of breathing occur in response to any condition affecting the pulmonary system (see Table 15-3). Breathing patterns can vary, depending on the neuromuscular or neurologic disease or trauma (Box 15-2).

In a large cross-section of people and clinical disorders, hypoventilation is one of the most common changes in breathing patterns observed. Anything that can cause hypoxemia (e.g., fever, malnutrition, metabolic disturbance, loss of blood or blood flow, or availability of oxygen) reduces energy supplies and results in respiratory muscle dysfunction and altered breathing patterns. When hypoxemia is accompanied by skeletal muscle atonia associated with any neuromuscular cause, hypoventilation may further jeopardize the ventilatory pump.

Breathing pattern abnormalities seen with head trauma, brain abscess, diaphragmatic paralysis of chest wall muscles and thorax (e.g., generalized myopathy or neuropathy), heat stroke, spinal meningitis, and encephalitis can include *apneustic breathing*, *ataxic breathing*, or *Cheyne-Stokes respiration* (CSR). Apneustic breathing localizes damage to the midpons and is most commonly a result of a basilar artery infarct. Ataxic, or Biot's, breathing is caused by disruption of the respiratory rhythm generator in the medulla. CSR may be evident in the well older adult, as well as in compromised clients. The most common cause of CSR is severe congestive heart failure, but it can also occur with renal failure, meningitis, drug overdose, and increased intracranial pressure. It may be a normal breathing pattern in infants and older persons during sleep.

Spinal cord injuries above C3 result in loss of phrenic nerve innervation, necessitating a tracheostomy and ventilatory support. *Ventilatory support* is used to refer to a variety of interventions, including mechanical ventilation via endotracheal intubation, noninvasive ventilatory support with continuous positive airway pressure (CPAP), positive end-expiratory pressure (PEEP), and bilevel positive airway pressure (BiPAP). See reference 140 for a complete description of the various means of ventilatory support.

Clients with generalized weakness, as in the Guillain-Barre syndrome, some myopathies or neuropathies, or incomplete spinal cord injuries, may show a tendency toward a specific breathing pattern called *lateral-costal breathing* (see Table 15-3).

SPECIAL IMPLICATIONS FOR THE THERAPIST

15-1

Signs and Symptoms of Pulmonary Disease

Many people with neuromusculoskeletal conditions, as well as people with primary or secondary pulmonary pathology, have the potential for oxygen trans-

Continued.

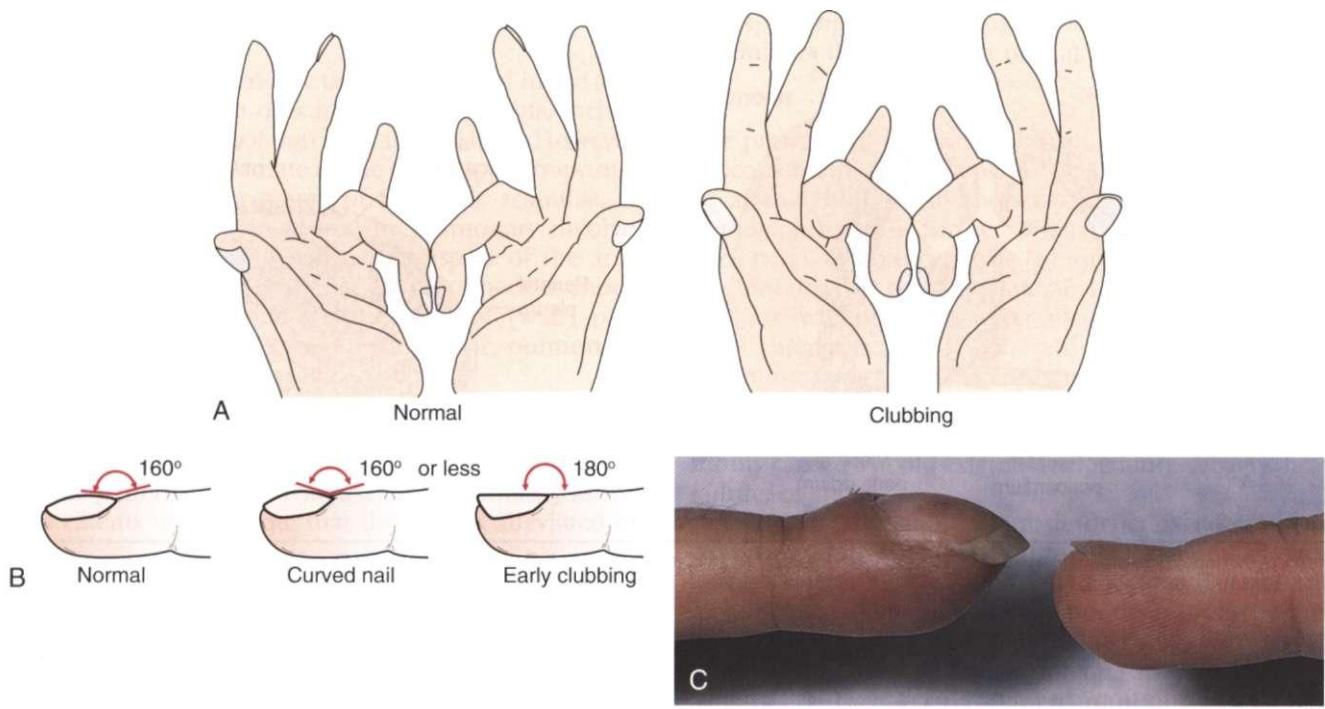


Figure 15-4

A, Assessment of clubbing by the Schamrath method. The client places the fingernails of opposite fingers together and holds them up to a light. If a diamond shape can be seen between the nails, there is no clubbing. **B**, The profile of the index finger is examined, and the angle of the nail base is noted; it should be about 160 degrees. The nail base is firm to palpation. Curved nails are a variation of normal with a convex profile and may look like clubbed nails, but the angle between the nail base and the nail is 160 degrees or less. In early clubbing, the angle straightens out to 180 degrees and the nail base feels spongy to palpation. **C**, Photograph of advanced clubbing of the finger (left) compared with normal finger (right). (A and B, from Swartz MH: *Textbook of physical diagnosis: history and examination*, Philadelphia, 1989, WB Saunders; C, from Swartz MH: *Textbook of physical diagnosis: history and examination*, ed 5, Philadelphia, 2006, WB Saunders)

port deficits (and their sequelae discussed previously), impaired ventilation, and altered breathing patterns. For each type of condition, the therapist must identify those steps in the oxygen transport pathway that are affected so that intervention targets the specific underlying problem as much as possible.

Monitoring the cardiopulmonary status is important because many of the interventions provided by a therapist elicit an exercise stimulus and stress the oxygen transport system. Because impairment can result from diseases other than cardiopulmonary conditions, therapists in all settings need expertise in anticipating and detecting pulmonary dysfunction in the absence of primary pulmonary disease.¹¹¹⁻¹⁴⁰

Recognizing abnormal responses to interventions is important in identifying the client who needs additional intervention or who needs to be referred to another health care professional. For an excellent review of the oxygen transport deficits concept and more detailed implications by system, see reference 111.

Clinical observation of the client as he or she breathes is important (Box 15-3) and can alert the therapist to respiratory pathologic conditions. Assessment of the muscle groups (abdominal and intercostal muscles, accessory muscles, and the diaphragm) involved in normal ventilatory function may be required. Techniques to improve ventilation can

enhance motor performance and improve a client's functional level. The reader is referred to more specific texts for information about intervention techniques.^{140,198}

High blood pressure in the pulmonary circulation (pulmonary hypertension) can cause pain during exercise that is often mistaken for cardiac pain (angina pectoris). For the therapist, musculoskeletal causes of chest pain must be differentiated from pain of cardiac, pulmonary, epigastric, and breast origins before treatment intervention begins.¹⁷² The therapist involved in performing airway clearance techniques and pulmonary rehabilitation must recognize precautions for and contraindications to therapy interventions in the medical client (Table 15-4).

AGING AND THE PULMONARY SYSTEM

Aging affects not only the physiologic functions of the lungs (ventilation and respiration) but also the ability of the respiratory system to defend itself. More than any other organ, the lung is susceptible to infectious processes and environmental and occupational pollutants (see the section on Environmental and Occupational Dis-

Box 15-2**BREATHING PATTERNS AND ASSOCIATED CONDITIONS****Hyperventilation**

- Anxiety
- Acute head injury
- Hypoxemia
- Fever

Kussmaul's Respiration

- Strenuous exercise
- Metabolic acidosis

Cheyne-Stokes Respiration

- Congestive heart failure
- Renal failure
- Meningitis
- Drug overdose
- Increased intracranial pressure
- Infants (normal)
- Older people during sleep (normal)

Hypoventilation

- Fibromyalgia syndrome
- Chronic fatigue syndrome
- Sleep disorder
- Muscle fatigue
- Muscle weakness
- Malnutrition
- Neuromuscular disease
 - Guillain-Barré
 - Myasthenia gravis
 - Poliomyelitis
 - Amyotrophic lateral sclerosis (ALS)
- Pickwickian or obesity hypoventilation syndrome
- Severe kyphoscoliosis

Apneustic

- Midpons lesion
- Basilar artery infarct

Biot's Respiration (Ataxia)

- Exercise
- Shock
- Cerebral hypoxia
- Heat stroke
- Spinal meningitis
- Head injury
- Brain abscess
- Encephalitis

eases in this chapter). These factors, combined with the normal aging process, contribute to the decline of lung function.

Age-related alterations in the respiratory system are based on structural changes that lead to functional impairment of gas exchange.^{399,463} Chest wall compliance decreases with aging because of changes in joints of the ribs and spine, as well as alterations in collagen. This increased stiffness affects the volume of air moved and the WOB. Elastic recoil also is decreased by intermolecu-

Box 15-3**CLINICAL INSPECTION OF THE RESPIRATORY SYSTEM****Respiratory rate, depth, and effort of breathing**

- Tachypnea
- Dyspnea
- Gasping respirations

Breathing pattern or sounds (see also Table 15-3)

- Cheyne-Stokes respiration
- Hyperventilation or hypoventilation
- Kussmaul's respiration
- Lateral-costal breathing
- Paradoxical breathing
- Prolonged expiration
- Pursed-lip breathing
- Wheezing/rhonchi
- Crackles (formerly called *rales*)
- Gurgles (formerly called *rhonchi*)

Cyanosis

- Pallor or redness of skin during activity
- Clubbing (toes, fingers)

Nicotine stains on fingers and hands

- Retraction of intercostal, supraclavicular, or suprasternal spaces
- Use of accessory muscles
- Nasal flaring
- Tracheal tug

Chest wall shape and deformity

- Barrel chest
- Pectus excavatum
- Pectus carinatum
- Kyphosis
- Scoliosis

Cough

Sputum: frothy; red-tinged, green, or yellow

lar collagen crosslinks. Alveolar walls flatten, surface area is reduced, and the small airways more readily collapse and trap air, reducing the capacity for gas exchange.^{140,218} Thus diminished gas exchange is primarily due to increased physiologic dead space.

Many changes that occur with aging affect the lower airway, but in the upper airway the movement of the cilia slows and becomes less effective in sweeping away mucus and debris. This reduced ciliary action combined with the other changes noted predisposes the older client to increased respiratory infections.

Reduction in respiratory muscle strength and endurance and subsequent increase in WOB requiring greater muscle oxygen consumption at any workload are observed with increasing age.^{52,140} Respiratory muscle strength is measured by maximum inspiratory pressure and maximum expiratory pressure. These measurements have been correlated with spiroometry, nutritional status, and grip strength. Loss of respiratory muscle strength can lead to dyspnea and ultimately to ventilatory pump failure.

Normal minute ventilation of older adults is comparable to that of younger people, although tidal volumes are smaller and rate is higher. There is a significant blunting of response to hypoxia and hypercapnia from both the respiratory and cardiovascular systems, particularly at

Table 15-4 Considerations for and Contraindications to Airway Clearance Techniques in the Medical Client

Considerations	Contraindications
Hemoptysis	Untreated tension pneumothorax; treat when chest tube has been inserted and client is stable
Fragile ribs (e.g., metastatic bone cancer, osteoporosis, flail chest, rib fractures, osteomyelitis of the ribs)	Unstable cardiovascular system
Burns, open wounds, skin infections in thoracic area	Hypotension
Pulmonary edema, congestive heart failure	Uncontrolled hypertension
Large pleural effusion	Acute myocardial infarction
Pulmonary embolism (controversial)*	Arrhythmias
Symptomatic aneurysm or decrease in circulation of the main blood vessels	Conditions prone to hemorrhages (platelet count <20,000/mm ³ ; must have physician's approval)
Platelet count between 20,000 and 50,000/mm ³	Unstabilized head and neck injury
Postoperatively	Intracranial pressure >20 mm Hg
Neurosurgery (positioning may cause increased intracranial pressure; can begin gentle breathing exercises)	
Esophageal anastomosis (gastric juices may affect suture line)	
Orthopedic clients who are limited in positioning	
Recent spinal fusion	
Surgical complications (e.g., pericardial sac tear)	
Recent skin grafts or flaps	
Resected tumors (avoid tumor area)	
Recently placed pacemaker	
Older or nervous clients who become agitated or upset with therapy	
Acute spinal injury or recent spinal surgery such as laminectomy (precaution: log-roll and position with care to maintain vertebral alignment)	

*A question remains whether there may be a recurrence (repeat emboli in the medically unstable client, i.e., one whose blood level of anticoagulants is not yet adequate to prevent a possible second embolus from dislodging) with movement in positioning the client for airway clearance techniques. However, allowing the client to lie still can contribute to the development of further venous stasis.

rest. The hypercapnia response during exercise is greater in older adults, contributing to more dyspnea for a given workload even in the absence of oxygen desaturation or metabolic acidosis.

Most adults attain maximal lung function (as measured by forced expiratory volume [FEV]) during their early twenties, but with increasing age, especially after age 55 years, there is an overall decrease in the functional ability of the lungs to move air in and out. This decline peaks by age 75 years, falling to about 70% of our maximum. Aging reduces the reserve capacity of virtually all pulmonary functions regardless of lifestyle, although a sedentary lifestyle accelerates the decline in functional capacity.²⁴⁹

All of these changes contribute to the increased WOB, meaning that the older adult works harder for the same air exchange as the younger person. These changes are influenced by lifestyle and environmental factors, respiratory disease, and body size. The effects of age are not nearly as influential as the effects of smoking in causing a premature decline in lung function and in limiting the ability to exercise.

Pulmonary complications during anesthesia and the postoperative period are significantly increased in older adults with preexisting diseases. Loss of an effective cough reflex contributes to an increased susceptibility to pneumonia and postoperative atelectasis in the older population. Other contributing factors to the loss of an effective cough reflex include conditions more common in older age such as reduced consciousness, use of sedatives, impaired esophageal motility, dysphagia, and neurologic diseases.

SPECIAL IMPLICATIONS FOR THE THERAPIST 15-2

Aging and the Pulmonary System

The therapist practicing in a geriatric setting needs to be knowledgeable about the normal consequences of aging to be able to identify the origin of and differences between impairments of aging and pathology. The ability to measure and discriminate between the process of aging and the sequelae of pathologic conditions (including consideration of the impact of comorbidities) is essential in the management of impairment and prevention of functional decline. Descriptions of the normal progressive decline of the respiratory system and the physiologic effects of pathologic conditions (both acute and chronic) as these conditions relate to the aging adult are available.^{52,140,315} Appropriate test measures are available for this type of differential assessment.¹⁸⁰

Pulmonary Capacity and Exercise

Although ventilatory and respiratory functions of older adults undergo a process of change related to aging that begins in early adulthood, it does not appear that healthy older people are limited by these changes in exercise capacity for activities that require moderate levels of oxygen consumption (Vo_{2}). On the other hand, clients with obstructive lung disease have a significant loss of vital capacity and may experience SOB at relatively low exercise intensities. In fact, the older person with obstructive lung disease may self-limit exercise because of dyspnea as opposed to exercise limitation by reduced cardiovascular capacity. The

normal anatomic and physiologic changes associated with aging that reduce the pulmonary reserve capacity of older adults combine with COPD pathology to exaggerate the pulmonary symptoms associated with aging.

Exercise capacity or exercise tolerance does decrease in the older adult as the PaO_2 (measure of oxygen in arterial blood) decreases. Daily physical activity can be assessed using the following categories: sedentary; sedentary with some daily activity; active through occupation or recreational activity; and trained athlete. A higher level of habitual physical activity is one factor favorably influencing oxygen delivery.

The ability to deliver oxygen to the tissues is called *maximal Vo_2* (Vo_{max}) and reflects the functioning of the oxygen transport pathway. Age-associated reductions in cardiac output may compromise the ventilation/perfusion balance, and the PaO_2 (and thus oxygen delivery) may be reduced even more.

Regular exercise can substantially slow the decline in Vo_{max} delivery caused by cardiovascular deconditioning related to age or lowered levels of habitual physical activity. Decreases in respiratory muscle strength and endurance occurring with age can be enhanced with exercise, although much of the improved ventilatory efficiency has been attributed to peripheral changes (decreased carbon dioxide production and blood lactate).⁴⁴³ In other words, peripheral conditioning improves function but does not make changes in the lung parenchyma.

Weight loss appears to alter static lung volumes, suggesting that some of the changes in lung function associated with aging may be a result of the development of obesity and therefore modifiable with diet and exercise.⁴⁵⁰ A sedentary lifestyle contributes to the normal loss of muscle mass that occurs with aging. This loss of muscle mass contributes to reduced exercise capacity and deconditioning. These changes can be slowed by exercise training.

INFECTIOUS AND INFLAMMATORY DISEASES

Pneumonia

Overview and Etiologic Factors

Pneumonia is an inflammation affecting the parenchyma of the lungs and can be caused by (1) a bacterial, viral, fungal, or mycoplasmal infection (organisms that have both viral and bacterial characteristics); (2) inhalation of toxic or caustic chemicals, smoke, dusts, or gases; or (3) aspiration of food, fluids, or vomitus. It may be primary or secondary, and it often follows influenza. The common feature of all types of pneumonia is an inflammatory pulmonary response to the offending organism or agent. This response may involve one or both lungs at the level of the lobe (lobar pneumonia) or more distally at the bronchioles and alveoli (bronchopneumonia).

Routes of Infection

The major routes of infection are airborne pathogens, circulation, sinus or contiguous infection, and aspiration. Nosocomial infections have twice the mortality and morbidity of non-hospital-acquired infections.³¹⁸

Incidence

Pneumonia is a commonly encountered disease with more than 4 million cases diagnosed each year. Combined cost of pneumonia and influenza to the U.S. economy was \$37.5 billion in 2004.³⁴⁴ It is a leading cause of death in the United States, claiming the lives of approximately 65,000 Americans annually. Approximately 30% of pneumonias are bacterial and especially prevalent in the older adult. Viral pneumonia, accounting for nearly one-half of all cases, is not usually life-threatening except in the immunocompromised person. The remaining 20% of all cases are caused by mycoplasma.

Risk Factors

Infectious agents responsible for pneumonia are typically present in the upper respiratory tract and cause no harm unless resistance is lowered by some other factor. Many host conditions promote the growth of pathogenic organisms, but cigarette smoking (more than 20 cigarettes/day) is highly correlated with community-acquired pneumonia.¹⁰ Pneumonia is also a frequent complication of acute respiratory infections such as influenza and sinusitis.

Other risk factors include chronic bronchitis, poorly controlled diabetes mellitus, uremia, dehydration, malnutrition, and prior existing critical illnesses such as chronic renal failure, chronic lung disease, or acquired immunodeficiency syndrome (AIDS). In addition, the stress of hospitalization, confinement to an extended care facility or intensive care unit, surgery, tracheal intubation, treatment with antineoplastic chemotherapy or immunosuppressive drugs, and urinary incontinence promotes rapid colonization of pathogenic organisms.

Infants, older adults, people with profound disabilities or who are bedridden, and persons with altered consciousness (e.g., caused by alcoholic stupor, head injury, seizure disorder, drug overdose, or general anesthesia) are most vulnerable. Inactivity and immobility cause pooling of normal secretions in the airways that creates an environment promoting bacterial growth. People with severe periodontal disease, those who have difficulty swallowing, those who have an inability to take oral medications, or those whose cough reflexes are impaired by drugs, alcohol, or neuromuscular disease are at increased risk for the development of pneumonia as a result of aspiration.

Pathogenesis

Although a common disease, pneumonia is relatively rare in healthy people because of the effectiveness of the respiratory host defense system and the fact that healthy lungs are generally kept sterile below the first major bronchial divisions. In the compromised person, the normal release of biochemical mediators by alveolar macrophages as part of the inflammatory response does not eliminate

invading pathogens. The multiplying microorganisms release damaging toxins stimulating full-scale inflammatory and immune responses with damaging side effects.

Endotoxins released by some microorganisms damage bronchial mucous and alveolocapillary membranes. Inflammation and edema cause the acini and terminal bronchioles to fill with infectious debris and exudate so that air cannot enter the alveoli and gas exchange is impaired, leading to ventilation/perfusion abnormalities and dyspnea. With the appearance of an inflammatory response, clinical illness usually occurs. Production of interleukin-1 (IL-1) and tumor necrosis factor (TNF) by alveolar macrophages can contribute to many of the systemic effects of pneumonia such as fever, chills, malaise, and myalgias.

Resolution of the infection with eventual healing occurs with successful containment of the pathogenic microorganisms. However, little is known about the actual processes that halt the acute inflammatory reaction in pneumonia and initiate recovery.

Aspiration Pneumonia. The risk of aspiration pneumonia occurs when anatomic defense mechanisms are impaired such as occurs with seizures; a depressed central nervous system (CNS) inhibiting the cough reflex; recurrent gastroesophageal reflux; neuromuscular disorders, especially with suck-swallow dysfunction; anatomic abnormalities (laryngeal cleft or tracheoesophageal fistula); and debilitating illnesses. Chronic aspiration often causes recurrent bouts of acute febrile pneumonia. Although any region may be affected, the right side, especially the right upper lobe in the supine person, is commonly affected because of the anatomic configuration of the right main-stem bronchus.

Fungal Pneumonia. Pneumonia caused by fungi may present with mild symptoms, though some people become very ill. The three most common types, *histoplasmosis*, *coccidioidomycosis*, and *blastomycosis*, are generally specific to a limited geographic area. Other fungal lung infections primarily affect people with compromised immune systems. Diagnosis is made by culturing sputum samples.

Viral Pneumonia. Viral pneumonia is usually mild and self-limiting, often bilateral and panlobular but confined to the septa rather than the intraalveolar spaces as is more likely with bacterial pneumonia. Viral pneumonia can be a primary infection creating an ideal environment for a secondary bacterial infection, or it can be a complication of another viral illness such as measles or chickenpox. The virus destroys ciliated epithelial cells and invades goblet cells and bronchial mucous glands. Bronchial walls become edematous and infiltrated with leukocytes. The destroyed bronchial epithelium sloughs throughout the respiratory tract, preventing mucociliary clearance.

Bacterial Pneumonia. Destruction of the respiratory epithelium by infection with the influenza virus may be one mechanism whereby influenza predisposes people to bacterial pneumonia. The lung parenchyma, especially the alveoli in the lower lobes, is the most common site of bacterial pneumonia. When bacteria reach the alveolar surfaces, most are rapidly ingested by phagocytes.

Once phagocytosis has occurred, intracellular lysis proceeds but at a slower rate for bacteria than for other particles. As the condition resolves, neutrophils degenerate and macrophages appear in the alveolar spaces, which ingest the fibrin threads, and the remaining bacteria in the respiratory bronchioles are then transported by lung lymphatics to regional lymph nodes. The infection is usually limited to one or two lobes.

Clinical Manifestations

Most cases of bacterial pneumonia are preceded by an upper respiratory infection (URI), frequently viral. Signs and symptoms of pneumonia include sudden and sharp pleuritic chest pain aggravated by chest movement and accompanied by a hacking, productive cough with rust-colored or green purulent sputum. Other symptoms include dyspnea, tachypnea accompanied by decreased chest excursion on the affected side, cyanosis, headache, fatigue, fever and chills, and generalized aches and myalgias that may extend to the thighs and calves. Older adults with bronchopneumonia have fewer symptoms than younger people, and 25% remain afebrile because of the changes in temperature regulation as part of the normal aging process. Associated changes in gas exchange (hypoxia and hypercapnia) may result in altered mental status (e.g., confusion) or loss of balance and may lead to falls.

Most cases of pneumonia are relatively mild and resolve within 1 to 2 weeks, although symptoms may linger for 1 or 2 more weeks (more typical of viral or mycoplasma pneumonia). If the infection develops slowly with a fever so low as to be unnoticeable, the person may have what is referred to as "walking pneumonia." This form tends to last longer than any other form of pneumonia. Complications of pneumonia can include pleural effusion (fluid around the lung), empyema (pus in the pleural cavity), and more rarely, lung abscess.

MEDICAL MANAGEMENT

DIAGNOSIS. The clinical presentations of pneumonias caused by different pathogenic microorganisms overlap considerably, requiring microscopic examination of respiratory secretions in making a differential diagnosis. Gram stain, color, odor, and cultures are part of the sputum analysis. A blood culture may help identify the bacteria, but bacterial counts are only positive in approximately 10% of bacterial pneumonias; 90% of bacterial pneumonias do not show a positive bacterial count.

The U.S. Food and Drug Administration (FDA) has approved a simple, quick urine test (urinary antigen testing) for detecting *Streptococcus pneumoniae* that provides results in 15 minutes. Immediate test results allow specific treatment to begin right away, thus controlling antibiotic overuse and antibiotic resistance with cost-effective targeted antibiotics. Results of the urine test should be confirmed with a culture. Research continues to develop new diagnostic techniques (e.g., polymerase chain reaction testing) to determine the microbiologic etiology of pneumonia.