HEREDITARY SPHEROCYTOSIS

HS is the **most common inherited** cause of hemolysis due to RBC membrane disorder with a wide spectrum of severity. The genetic mutation is usually transmitted as **AD & less as AR**; new mutations are common (≈ 25%).

Path. HS is due to a molecular defect in spectrin or ankyrin which are the major components of cytoskeleton responsible for RBC shape result in reduction of deformability of RBCs then destruction in the spleen.

C.M.

- HS may be one of the causes of **hemolytic diseases of newborn**
- The severity of symptoms in infants and children is **variable**. Some children remain **asymptomatic** into adulthood, whereas others may have **severe** anemia, jaundice, and fatigue.

Severe cases may be marked by expansion of medullary bones, splenomegaly, & gallstones (although usually asymptomatic).

Cx.

- **Aplastic crisis** is mainly due to Parvovirus-B19 infection which may cause reticulocytopenia & profound anemia which can result in high- output HF.
- **Rare** long-term Cxs may include: splenic sequestration crisis, gout, cardiomyopathy, priapism, leg ulcers, and spinocerebellar degeneration.

Inv.

- **Indirect** hyperbilirubinemia.
- **US of abdomen** may reveal the gallstones as early as 4 yr of age.
- **X-ray** of bones show BM expansion.
- **CBP** show **spherocytosis** of RBCs which appear smaller in diameter and hyperchromic with polychromatophilic reticulocytes. Hb is low or normal, MCV is normal, but MCHC is high.
- **BM exam** show erythroid hyperplasia.
- **Osmotic Fragility Test**; it can be done by incubation of RBCs in a progressive dilutions of iso-osmotic buffered salt solution, this make spherocytes to swell and lyse more readily in hypotonic solutions; it can be accentuated by depriving RBCs from glucose overnight at 37°C *(incubated osmotic fragility test).* However, this test is not sensitive or specific for HS.
- **Other tests** that have high sensitivity & specificity include: DNA analysis, cryohemolysis test, osmotic gradient ektacytometry, and eocin- 5-maleimide test.

D.Dx. Other rare causes of spherocytosis include: Wilson disease, thermal injury, & clostridial septicemia

Rx.
 Folic acid supplementation, 1 mg/day.
 Splenectomy is indicated when there is evidence of **severe** hemolysis (Hb <10 g/dl, reticulocyte count >10%), or when other **Cxs** are present e.g. aplastic crises, poor growth, cardiomegaly.
Splenectomy is usually recommended after 6 yr of age to avoid the heightened risk of postsplenectomy sepsis in younger children.
Patient should receive vaccines against pneumococcus, meningococcus & *H. influenzae* type b 2 wks before splenectomy.
After splenectomy, patient should also receive prophylactic oral penicillin V indefinitely.
Partial splenectomy may be indicated for children < 5 yr to preserve some immune function.
Note: *After splenectomy, there will be transient thrombocytosis & improvement of osmotic fragility test.*

AUTOIMMUNE HEMOLYTIC ANEMIAS

AIHA are associated with **3 types of autoantibodies**: Warm, Cold & Drug-induced. All are characterized by **positive direct antiglobulin *(Coombs)* test** which can detects coating of RBC surface by the immunoglobulins

- ***Warm Antibodies:-***

Et. Either primary (idiopathic) or secondary to other diseases e.g. Lymphoproliferative disorders, Connective tissue disorders (especially SLE), Chronic inflammatory diseases (ulcerative colitis), & Malignancies.
Path. These antibodies are **active at 35–40°C** *(warm antibodies)* and most often belong to **IgG** class (which **do not require complement** for activiation

Inv.
 CBP; usually **severe anemia** (Hb <6 g/dl) with **spherocytosis** and nucleated RBCs. **Reticulocytes may be >50%** .
 Direct Coombs test is **strongly +ve** and **indirect** Coombs test may also +ve.

Rx.
 Mild disease do not require specific therapy, whereas **severe** one require corticosteroids e.g. **Prednisone 2 (up to 6) mg/kg**, then taper*ring*

 Blood transfusion may be required for severe anemia (although it is only of transient benefit
 Severe hemolysis **resistant** to corticosteroids may need **IVIG, Rituximab, or Splenectomy.**

❖ *Cold Antibodies:-*

It can be divided into 2 types; cold agglutinin disease & paroxysmal cold hemoglobinuria.
 Cold Agglutinin disease is usually mediated by **IgM** class (which **requires complement** for activity, especially C1. These antibodies are usually **active at low body temp (<37°C**
Et. It is either primary (idiopathic) or secondary to other diseases e.g. Lymphoproliferative disorders or infections (especially *Mycoplasma pneumoniae* & Epstein-Barr virus).
C.M. The manifestations of hemolysis usually develop after exposure to cold; it usually acute & self-limited hemolysis which may be intravascular or extravascular.

Rx. Patient should **avoid exposure to cold** with **Rx of underlying** disease or infection. Corticosteroids & splenectomy are much less - effective, but immunosuppression (e.g. Rituximab) & plasmapheresis may be effective.
 Paroxysmal Cold Hemoglobinuria is usually mediated by **IgG** class Most cases are self-limited & usually associated with nonspecific viral infections. **Rx** by avoidance of cold & blood transfusion for severe anemia.

HEMOSTASIS

The main components of the hemostatic process are the vessel wall, platelets, coagulation proteins, anticoagulant proteins, and fibrinolytic system.

• Tests of Platelet disorders:-

1. ***Platelet Count:*** **Thrombocytopenia** is the most common acquired cause of bleeding disorder in children. N.R.: **$150\text{-}450 \times 10_3/mm_3$**.
2. ***Bleeding Time:*** It assesses **platelets and VWF disorders**. N.R.: **4-8 min**.
3. ***Platelet Aggregation:*** It assess **platelets function** through their aggregationin in vitro
4. ***Platelet Function Analyzer (PFA-100):*** It also assess **platelet adhesion-aggregation**

▯ Tests of Coagulation factors disorders:-

1. ***Prothrombin Time (PT):*** It measures the factors of **extrinsic pathway** .PT measures only the following factors: **1, 2, 5, 7, & 10**
N.R.: **≈ 10-13 sec**
2. ***Activated Partial Thromboplastin Time (aPTT or PTT):*** It measures the factors of **intrinsic pathway** ***Note.*** PTT measures the following factors: **1, 2, 5, 8, 9, 10, 11, 12 & VWF**.
N.R.: **≈ 25-40 sec**
3. ***Thrombin Time (TT):*** It measures the **final step** in the clotting cascade, in which fibrinogen is converted to fibrin.
N.R.: **11–15 sec**.

❖ *General approach to patient with bleeding tendency:-*

Hx. It is the most valuable, take details about the site, severity, previous surgery, menstrual, and family hx.
Ex. Generally, mucocutaneous bleeding is caused by platelets disorders or VWD, whereas deep bleeding into muscles and joints is caused by clotting factors deficiency.
Inv. Do 1st **Platelet count, PT, & PTT**. If abnormal, do **specific factor work-up**, whereas if normal, do **VWF testing & Thrombin time**.

HEMOPHILIA A & B

These are the **most common severe inherited** bleeding disorders that due to deficiencies of **F8 (85%) & F9 (15%)** respectively. These are **XL disorders**, but **female** can also be affected if she is homozygous or by Lyon hypothesis. **Spontaneous mutation** is common.
C.M. It depend on the degree of deficiency as follows:-
▯ ***Mild*** *deficiency;* factor level **>5%** of normal, it may be **asymptomatic** for many years or require **significant** trauma to bleed.
▯ ***Moderate*** *deficiency;* **1-5%**, it require a **minor** trauma.
▯ ***Severe*** *deficiency;* **<1%**, there may be **spontaneous** bleeding.
Bleeding, including intracranial hemorrhage, can occur **before** (in fetus) or **at birth**, but more commonly **after circumcision** in ≈ 30% of affected males; however, the most common manifestations of hemophilia is bleeding into joints or muscles.
Hemarthrosis is mainly occur in **large joints**, especially ankles, knees and elbows; when bleeding is repeated in only 1 joint, this will be the ***"target joint"*** which eventually result in **erosion** of that joint.

Hematoma of muscles e.g. **iliopsoas** may cause hypovolemic shock, vague area of **referred pain** in groin; the **hip** is held in flexed, internally rotated position. It can be diagnosed US or CT scan of iliopsoas muscle.
Life-threatening hemorrhage & shock may also occur in **any organ** or system e.g. CNS, GIT, RT...etc.
Inv.
 PTT is prolonged 2-3 times above the normal range, whereas other screening tests are usually normal (including PT).
 Specific F8 or F9 assay is used to confirm the Dx.
 Hemophilia carriers (e.g. other family members) can be screened by **Genetic studies** or **F8:VWF ratio**.
Rx. Early appropriate therapy is the hallmark of excellent hemophilia care.
❖ ***Desmopressin Acetate (DDAVP) Nasal Spray*** can be used **only** to treat patient with **mild hemophilia A** (not B) in dose, 150 μg (1 puff) for patients <50 kg & 300 μg (2 puffs) if >50 kg.
❖ ***Specific Factor (F8 or F9) Concentrate:*** The dose of each as follows:-
F8 = % of activity desired × body weight × 0.5
F9 = % of activity desired × body weight × 1.4
For **mild to moderate** bleeding, their levels of must be raised to hemostatic range (**35–50%** of activity); whereas for **major or life-threatening** hemorrhages, the dose should be raised up to **100%** of activity.
However, there are specific situations that require specific doses of F8 in hemophilia A; whereas in hemophilia B, F9 dose should be ↑ upto 50- 100% of below doses:-
 Major surgery or life-threatening hemorrhage; 50–75 IU/kg,
 Iliopsoas hemorrhage; 50 IU/kg, then half the dose every 12 hr until resolution.
 Hemarthrosis; 40 IU/kg on day 1, then half the dose until resolution. Bleeding into the hip joint may require aspiration.
 Muscle or significant SC hematoma; 20 IU/kg, may need every-other-day Rx until resolved.
 Mouth bleeding, tooth extraction or epistaxis; 20 IU/kg, antifibrinolytic Rx (e.g. aminocaproic acid); apply pressure.
 Hematuria; 20 IU/kg, Bed rest, Prednisone!.

❖***Supportive Care;*** include:-

 Hemophilia may require a comprehensive **Hemophilia Care Center** which involves a **team** of many specialists.
 Education of the patient & his family about the disease, its Rx & Cxs; with psychological support.
 Avoidance of trauma (including IM injection) or any violent contact sports with anticipatory guidance.
 Avoidance of Aspirin & other NSAI drugs.
 Vaccination againt HBV with periodic **screening** for blood-borne infections.
 Gene therapy is a promising therapy (in the future) for hemophilia.
Px. Bleeding can be prevented by giving the specific factor every other day (or every 3 days) to maintain a measurable clotting factor(>1% trough level). It used in 2 conditions:-
1. **Severe Hemophilia A or B** to prevent spontaneous bleeding
2. **Target joint** development.
Cx. Chronic arthropathy, Transfusion-transmitted infectious diseases, and ↓ response to Rx due to development of Inhibitors against F8 & F9.

❖ *Inhibitors:-*

These are **antibodies against F8 or F9** after repeated infusions that block their activities which manifested as **failure of bleeding to stop** after appropriate replacement therapy.
Rx.
1. **Desensitization programs**, in which **high doses of F8 or F9**
2. If desensitization **fails**, patient can be given **rituximab** (to ↓ Ab production) or factors that can bypass the inhibitor effect e.g. **recombinant aF7** (Novo7)

VON WILLEBRAND DISEASE

VWD is the **most common hereditary** bleeding disorder that affect ≈ **1- 2%** of population. It inherited as **AD** (homozygous is affected > heterozygous
VWF has 2 functions; 1st it adheres to subendothelial matrix after vascular damage & then it causes platelets to adhere to it through their glycoprotein IB (GPIb) receptor; the 2nd function it is a carrier protein for F8 in plasma.
C.M. VWD usually cause **mucocutaneous hemorrhage** e.g. excessive bruising, epistaxis, postoperative hemorrhage, and menorrhagia.

Note: *Menorrhagia may not be recognized as abnormal because other females in the family may also be affected with VWD, thus patient may present later on with iron deficiency anemia.*

Inv.

 Platelet function analysis is considered as a screening test for VWD.

 PTT & Bleeding Time are usually prolonged (although it may be normal in type 1 VWD). F8 activity measurement is also reduced in some types.

 VWF antigen.

 VWF structure

 Platelet count; **Genetic studies**.

Rx.

 Desmopressin acetate (DDAVP) nasal spray can ↑ VWF 3- to 5-folds

 Cryoprecipitate or **VWF concentrate** are effective in Rx of **all types of VWD**. Half life of both F8 & VWF is 12 hr.

 Aminocaproic acid can be used in epistaxis & dental extractions in dose 100 mg/kg loading dose orally followed by 50 mg/kg every 6 hrs; or by **Tranexamic acid**, 1300 mg orally ×3 daily for 5 days.

 In **severe bleeding**, patient should be given **platelets** (to replace the VWF in platelets), and **F8** (because endogenous correction of F8 require 12-24 hr).

IDIOPATHIC THROMBOCYTOPENIC PURPURA (Autoimmune Thrombocytopenia Purpura)

ITP is the **most common** cause of acute thrombocytopenia in a **well** child.

Et. Approximately 2/3 of cases occur **1–4 wk** after common **viral** infection (e.g. EBV) → **autoantibody** directed against platelet surface which is recognized by the Fc receptor on the splenic macrophages → their destruction; the reason for this response is **unknown**.

C.M. The classical presentation of ITP is **sudden** onset of generalized **petechiae & purpura** in a **previously healthy** child, **1–4 yr** old.

❖ Current classification system of ITP is according to the severity of bleeding (rather than platelet count) as follows:-

1. ***No*** symptoms.

2. ***Mild:*** mild bruising and petechiae, occasional minor epistaxis, very little interference with daily living.
3. ***Moderate:*** more severe skin and mucosal lesions, more troublesome epistaxis and menorrhagia.
4. ***Severe:*** severe bleeding episodes e.g. menorrhagia, epistaxis, melena that requiring transfusion or hospitalization, symptoms interfering seriously with quality of life.

Inv.

 ITP can be diagnosed **clinically** with the aid of **blood film** only that reveal **thrombocytopenia** (platelet count usually **<20 × 10^9/L**), platelet size is **normal or** ↑ (due to ↑ platelet turnover); whereas other cell lines (RBC & WBC) are typically normal.
 Other tests (e.g. BM exam) are only indicated when there is **abnormal physical finding** e.g. HSM or LAP (which are rarely may associated with ITP) or there is **abnormalities of blood film** e.g. anemia or leukopenia.

BM exam in ITP show normal or ↑ numbers of megakaryocytes, whereas other series are normal.

Rx. The **goal** of Rx is to elevate platelet count to **>20 × 10^9/L** (although
there is no correlation between platelet count & the severity of bleeding !).

 No therapy other than education and counseling can be used for **minimal, mild** and even **moderate symptoms.**
 ***IVIG;* 0.8–1 g/kg/day for 1–2 days** induces rapid rise in platelet count in 95% of patients within 2 days;
 ***IV Anti-D;* 50–75µg/kg once (but only for Rh+ve patients)** can ↑ platelet count in 80-90% of patient within 2-3 days; it acts by coating the RBC which then bind to macrophage Fc receptors and interfere with platelet destruction.
 ***Prednisone;* 1-4 mg/kg/day for 2–3 wk** (or until rise in platelet >20× 10^9/L) followed by rapid tapering.
 Platelet transfusion can only be used when there is intracranial or life- threatening bleeding (with the above therapies).
 Splenectomy should only be reserved for intracranial or life-threatening bleeding & for older children with chronic ITP.

Pg. 70-80% of ITP **resolves spontaneously within 6 mo** of illness, whereas only ≈ **20%** will persist **>1 yr** which is called ***"Chronic ITP".*** Here the patient should be re-evaluated for **diseases other than ITP** that associated with thrombocytopenia .

Rx of chronic ITP is as above, but may include **Rituximab**.

Splenectomy can induce remission in ≈ 75% of cases, but patient should receive pneumococcal and meningococcal vaccines before & penicillin px after splenectomy.
However, all of the above therapies neither affect short- nor long-term prognosis of ITP.

ACUTE LYMPHOBLASTIC LEUKEMIA

Epid. ALL is the **most common cause of malignancy in childhood**. It
mainly affects children between **2-3 yr** of age with **male** predominance.
Et. Idiopathic, although some are associated with **genetic syndromes**
e.g. Down, Bloom, and Fanconi syndrome
Environmental factors have also been implicated e.g. ionizing radiation, drugs **C.M.**
Hx. Initial presentation are usually nonspecific e.g. **anorexia, fatigue, malaise, irritability, and intermittent low-grade fever**. Bone pain or, less often, joint pain (especially of lower extremities) may be so severe that awake the patient at night.
Ex. LAP, splenomegaly +/_ hepatomegaly, deep tenderness of bones, testicular & joint swelling. In advanced cases, there is BM failure with **pallor** (due to anemia), **petechiae** (due to thrombocytopenia) & **fever** (due to infection after neutropenia).
Rarely, there may be evidence of ↑ ICP (due to CNS involvement) or respiratory distress (due to enlargement of anterior mediastinal LNs).
D.Dx. AML, NHL, Aplastic anemia, Infectious Mononucleosis, Systemic onset JIA, ITP…etc.
Inv.
 CBP show anemia and thrombocytopenia, however, atypical lymphocytes will be seen later on which can be in large number.
 BM aspiration & biopsy show lymphoblasts that represent >25% of BM cells.
 CSF exam is done for staging
 Flow cytometry, cytogenetics, and molecular studies may be done for classification & prognosis of ALL.
Rx.
 Remission induction for 4 wk by weekly vincristine, asparaginase & corticosteroids (dexamethasone or prednisone) with intrathecal cytarabine and/or methotrexate. This approach may cause remission in ≈98% of patients which is defined as <5% blasts in BM and return

of neutrophil and platelet counts to near-normal levels after ≈ 1 mo of Rx.
 CNS therapy is used to prevent later CNS relapses by repeated intrathecal chemotherapy
 Maintenance phase may lasts for 2-3 yr, it involves daily mercaptopurine and weekly methotrexate, usually with intermittent doses of vincristine and corticosteroids.
 Relapse should be treated with intensive chemotherapy with agents not previously used, followed by **Allogeneic Stem Cell Transplantation**.

Supportive Care for the acute & long-term Cxs of ALL should include:-
 Rx for **tumor lysis syndrome** by allopurinol or urate oxidase.
 Rx of **severe myelosuppression** by packed RBC & platelets.
 Sepsis require high index of suspicion with aggressive empirical antimicrobial therapy in febrile children with neutropenia. Patients must receive **Px against *Pneumocystis jiroveci* pneumonia** during and for several months after completing chemotherapy!.
Pg. Most children with ALL can now be expected to have survival rate >90% at 5 yr. However prognosis can be divided into favorable & unfavorable according to the following criteria:- - 281 -

Favorable	**Unfavorable**
✓ *Age* 1-10 yr	<1 or >10 yr
✓ *Initial leukocyte count* <50,000/ml	>50,000/ml
✓ *CNS metastasis* absent	present
✓ *Response to Rx* rapid (<1 mo)	slow
✓ *Relapse after Rx* late	early
✓ *Site of relapse* BM	CNS, testes
✓ *T-cell phenotype* absent	present

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ACUTE MYELOGENOUS LEUKEMIA

AML is much less common than ALL that usually occur in older children & adolescents
C.M. AML can be presented with **any or all manifestations of ALL**. Other features include:-
 CNS involvement is more common in AML than ALL.
 Discrete masses called *"Chloromas or granulocytic sarcomas"* usually seen in orbit or epidural space,.
 Subcutaneous nodules or *"blueberry muffin"* lesions (especially in infants) or infiltration of the gingival
 DIC

Inv. It is the **same as those of ALL**, except that BM show infiltration of >20% of fairly homogeneous population of blast cells.
Differentiation between ALL & AML can be done by staining the blast cells for **myeloperoxidase enzyme** which only present in AML. It also can be done by **Flow cytometry** that identify the subtypes of AML.
Rx.
 AML require aggressive multiagent chemotherapy to induce remission, thus unfortunately some patients die before remission can be achieved due to infection or bleeding after severe BM suppression.
 BM or stem cell transplantation after the 1st remission or after relapse is more effective than continued chemotherapy

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HODGKIN LYMPHOMA

HL is rare before 10 yr of age, but it is very **common in adolescents** & young adults with **male** predominance.
Et. Idiopathic. Some suggest **genetic predisposition** because some cases are cluster in families & the risk in monozygotic twins is 100-folds. Others are related to immunodeficiency & viral infection, especially EBV.
Path. HL appears to **arise from the lymphoid tissue** & spread to the adjacent LN in orderly fashion, although hematological spread can occur to many organs.
Reed-Sternberg cell is pathognomonic for HL). It is a large cell with multiple or multilobulated nuclei

C.M. HL can be presented with 1 or more of the following manifestations:-
 Commonly presented as painless, nontender, firm, rubbery, cervical (or supraclavicular) LAP.
 Manifestations of **airway obstruction** (dyspnea, hypoxia, cough), pleural or pericardial effusion due to mediastinal LAP.
 Manifestations of **BM infiltration** e.g. anemia, neutropenia, or thrombocytopenia.
 Hepatocellular dysfunction.
 Patients also exhibit **cellular immune system dysfunction** (which may persist even after recovery!).

 Systemic (B) symptoms are considered important in the staging of HL. It include: **unexplained fever >39$_0$C, drenching night sweats, and weight loss >10% of body weight over 3 mo.**

Inv. Any patient with persistent, unexplained LAP not associated with an obvious underlying inflammatory or infectious process should undergo **CXR**, if there is large mediastinal mass, then do **lymph node biopsy** (needle biopsy or preferably excisional biopsy). Other tests include: **CBP, ESR, serum Ferritin** (which is of some prognostic significance)**, LFT, CT or MRI of chest & abdomen, BM aspiration & biopsy.** It also may include **Bone scans** by either Gallium or FDG–PET imaging.
Rx. There are many chemotherapeutic regimens for HL, all are effective in eradicating of disease with **high cure rate**, especially if combined with radiotherapy
Patients who never achieve remission and those who experience early relapse are candidate for myeloablative chemotherapy +/_ radiation therapy followed by **allogeneic/autologous stem cell transplantation**.
Pg. Poor prognostic features include: big size of tumor, advanced stage of disease at diagnosis, presence of B symptoms, & early relapse (within 1 yr of Rx).

NON-HODGKIN LYMPHOMA

NHL is the **2nd most common** malignancy of childhood after ALL, usually occurs in older children & adolescents (between 5-19 yr).
Et. Idiopathic. Some are associated with genetic syndromes, immune-
deficiency, & viral infection, especially EBV & HIV.
C.M. & Classification:-
NHL can be divided into 4 subtypes, **most are of high grade** with aggressive clinical behavior & >70% of cases are present with advanced stages (3 or 4).
 Burkitt Lymphoma-BL (40%):
 Lymphoblastic Lymphoma-LL (30%):
 Diffuse Large B-Cell Lymphoma-
 Anaplastic Large Cell Lymphoma

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❖ NHL is characterized by **painless, rapid enlargement of lymph nodes**. Site-specific mass effect is depend on the region of body involved:-

 Thoracic involvement → cough, dyspnea, superior mediastinal synd.
 Abdominal involvement → rapidly enlarging and massive abdominal mass, intestinal obstruction, intussusception-like symptoms, ascites.
 Waldeyer ring involvement → nasal stuffiness, earache, hearing loss, tonsillar enlargement.
 Bone involvement → localized bone pain (primary or metastatic).
Inv. CBP, serum electrolytes, RFT, LFT, CXR, CT (or MRI), PET, CSF exam,
bilateral BM aspiration & biopsy.
The tumor should also be tested by **flow cytometry**

Rx. It is mainly involve **multiagent systemic & intrathecal chemotherapy**. **Radiation** therapy is used only in special circumstances; whereas **surgery** is used mainly for diagnosis and staging.
There are **many protocols** for each subtype of NHL except for localized ALCL which may require surgical resection alone!.

Supportive care include:-
 Tumor lysis syndrome is the most important Cx of therapy that require **vigorous rehydration** with **Allopurinol**, 10 mg/kg ÷ 3 orally or **Rasburicase**, 0.2 mg/kg once daily IV, both given for up to 5 days.
 Some patients require **G-CSF Px** to prevent fever and neutropenia following myelosuppressive chemotherapy with **antibiotics Px** to prevent infections.
 Indwelling **central venous catheters** routinely are placed to facilitate frequent blood draws, chemotherapy and transfusion administration, and for parenteral nutrition to prevent weight loss and nutritional debilitation.
Pg. Excellent for most cases of NHL. Patients with localized disease have a 90-100% chance of survival, whereas those with advanced disease have 70-95% chance