دکتر پیمان اعتمادی فر

فوق تخصص خون وسرطان اطفال

عضوهیئت علمی دانشگاه علوم پزشکی یاسوج

استادیار

هماتولوژی

Bleeding emergency

- **Life threatening hemorrhage in :**

1) **Hemophilia**
2) **ITP**
3) **DIC**

- **CNS hemorrhage**
- **GI bleeding**
- **Psoas muscle hemorrhage**

What is hemophilia?

- Hemophilia is an X-linked congenital bleeding disorder with a frequency of about one in 10,000 births.
- Hemophilia is caused by a deficiency of coagulation factor VIII (FVIII) (hemophilia A) or factor IX (FIX) (hemophilia B) related to mutations of the clotting factor gene.
- The number of affected persons worldwide is estimated to be about 400,000.

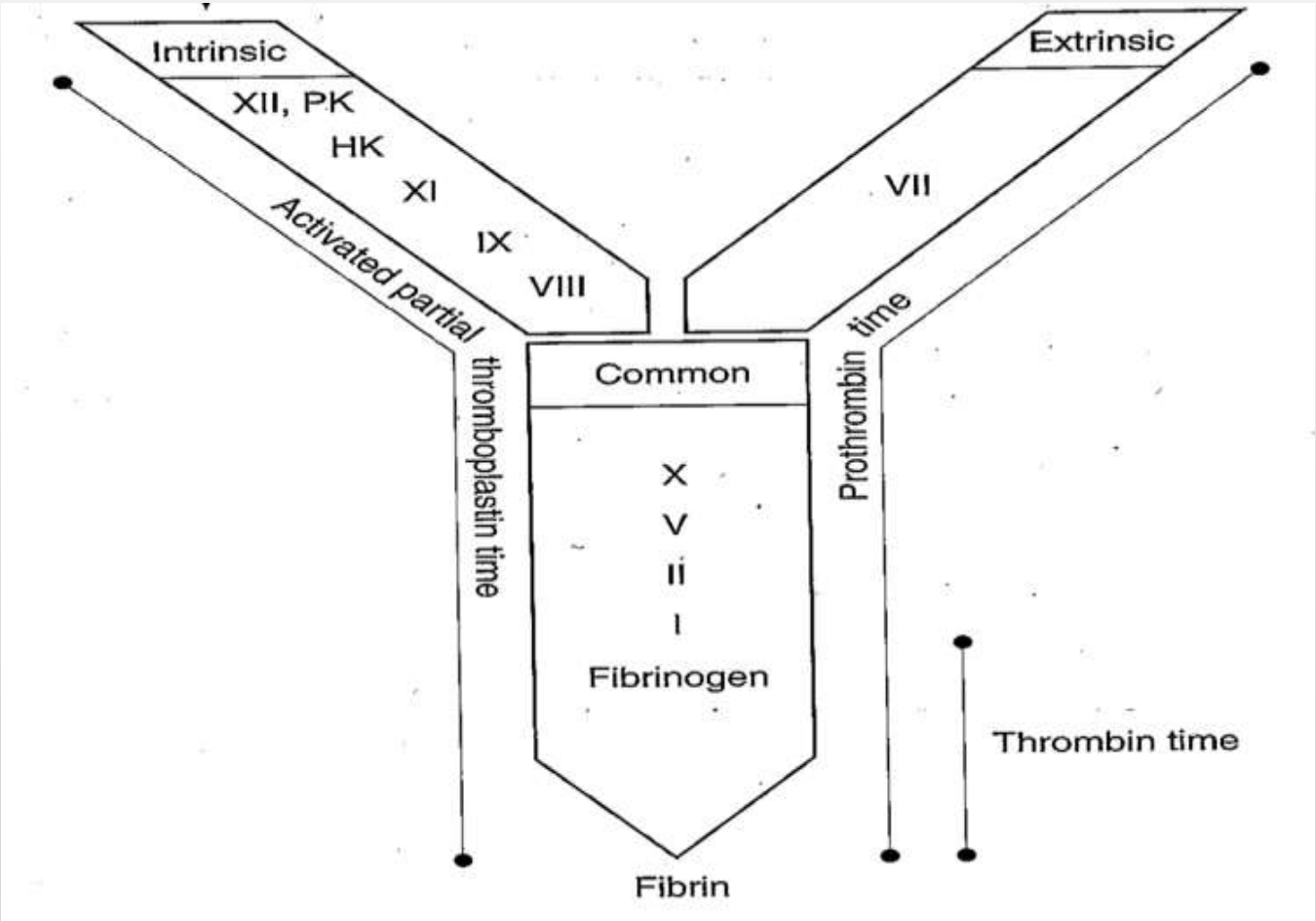
Classification of Hemophilia

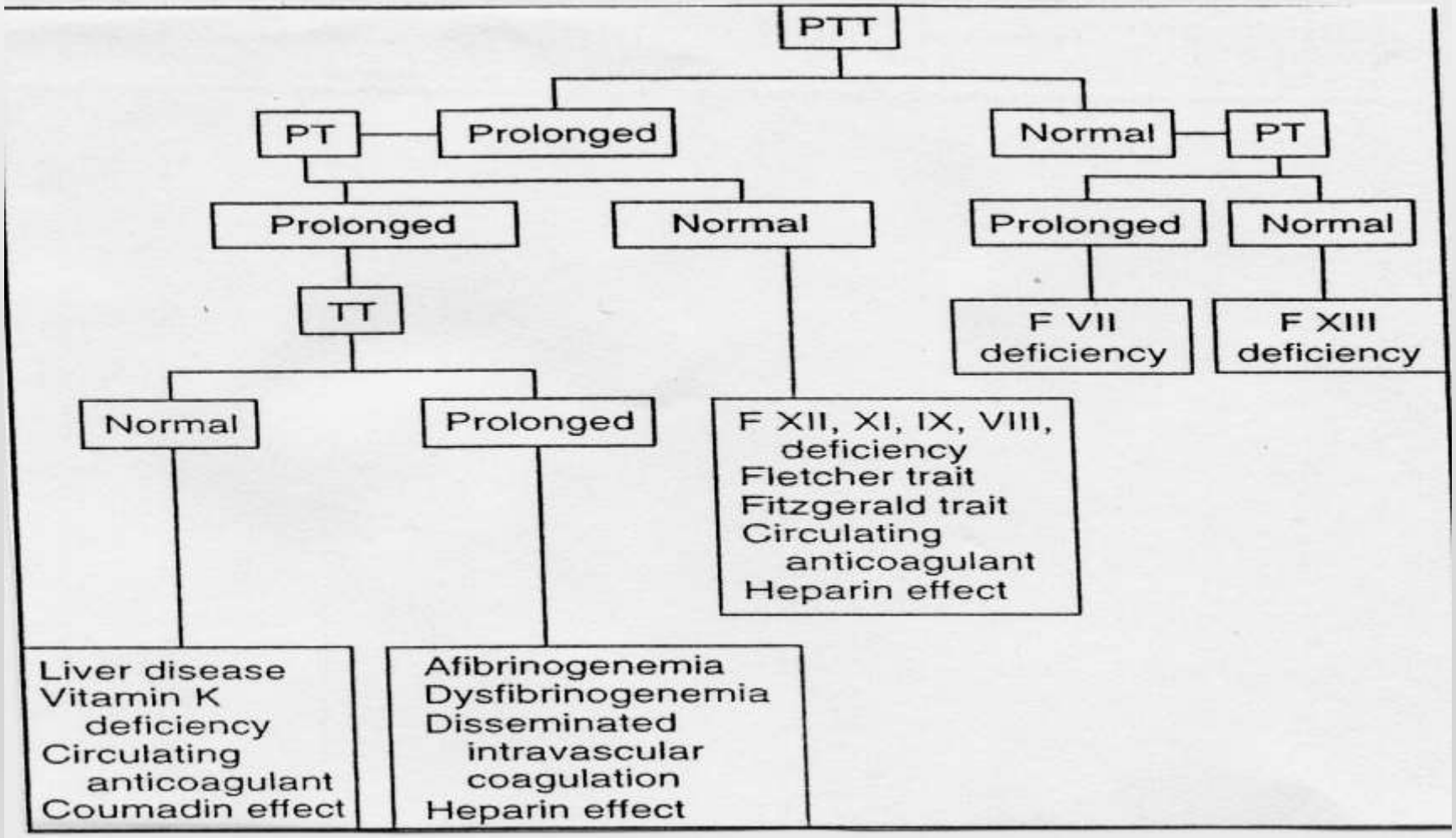
- **Severe <1% activity level - Spontaneous bleeds**
- **Moderate 1 to 5% activity --Trauma/surgery bleeds**

  Occasional joint bleeds
- **Mild 5 to 30% activity - Major trauma/surgery**

  Rare joint bleeds

Coagulation cascade




PTT
PT
Prolonged
Normal
PT
Prolonged
Normal
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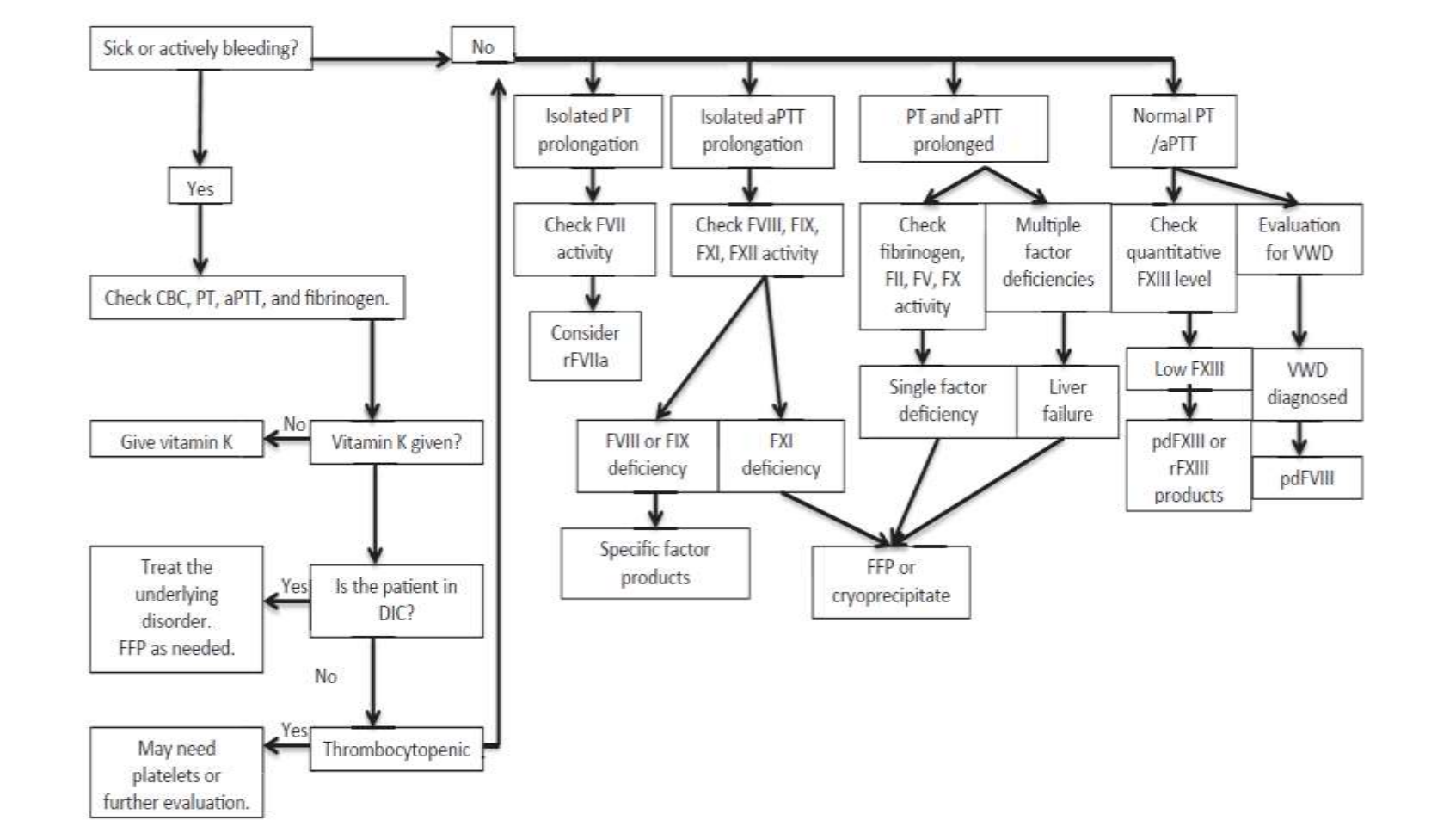
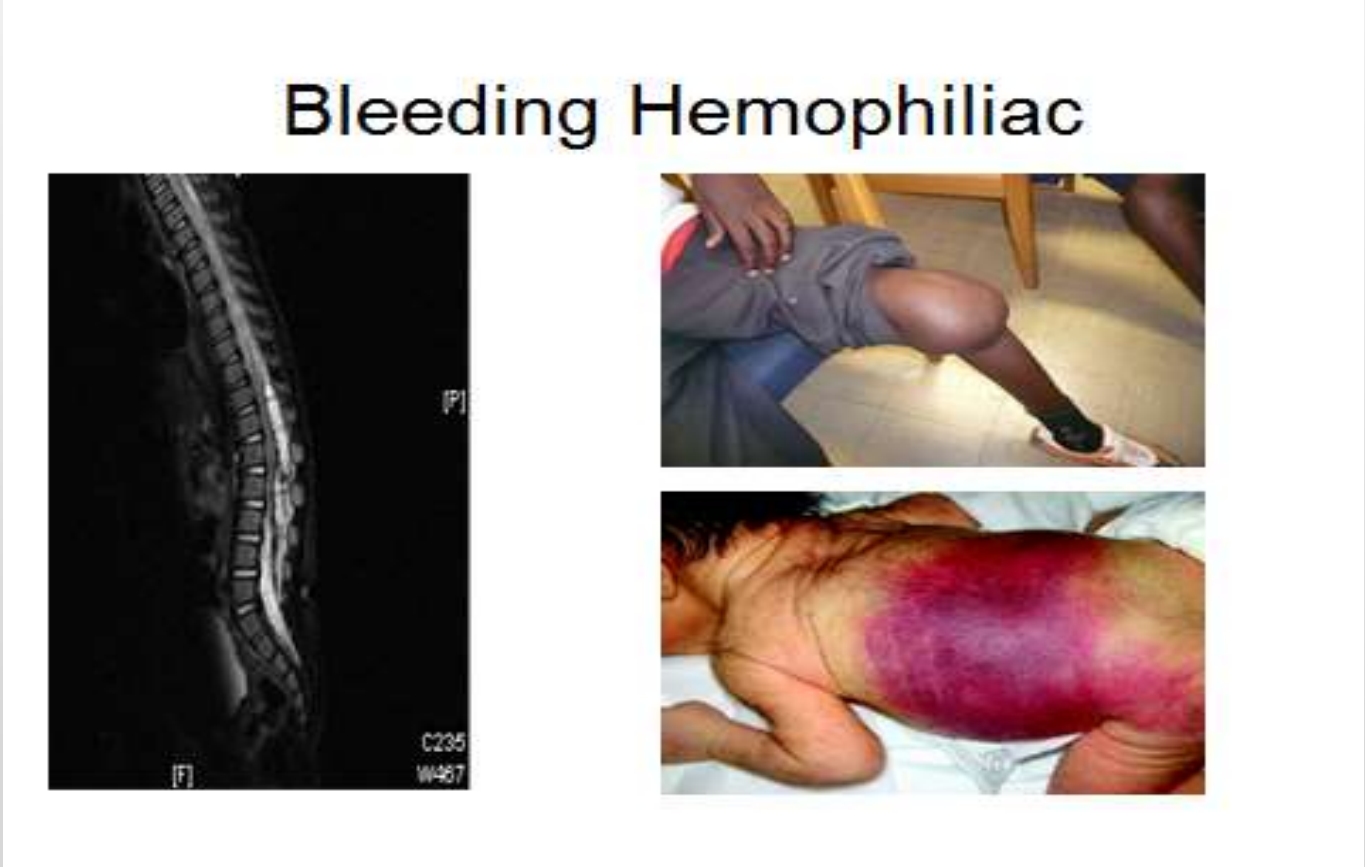
TT
F VII deficiency
F XIII deficiency
Normal
Prolonged
F XII, XI, IX, VIII, deficiency
Fletcher trait
Fitzgerald trait
Circulating anticoagulant
Heparin effect
Liver disease
Vitamin K deficiency
Circulating anticoagulant
Coumadin effect
Afibrinogenemia
Dysfibrinogenemia
Disseminated intravascular coagulation
Heparin effect

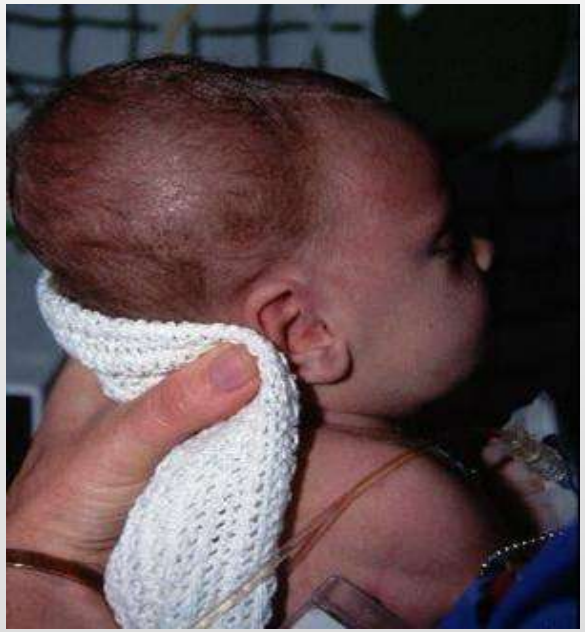
Algorithm for the approach to a bleeding neonate

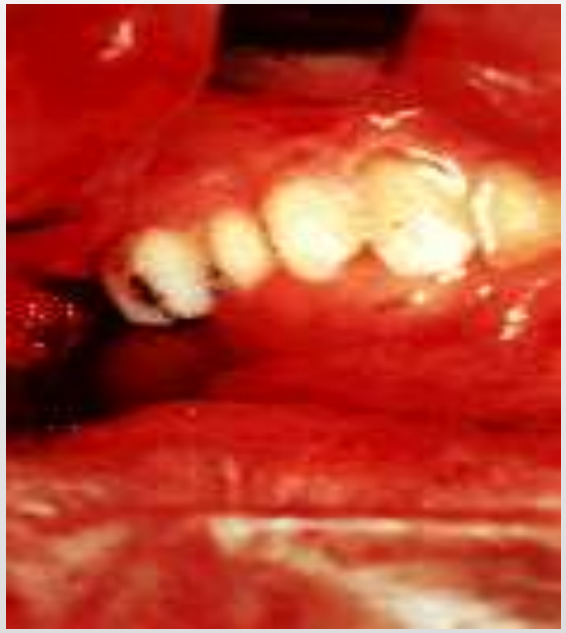


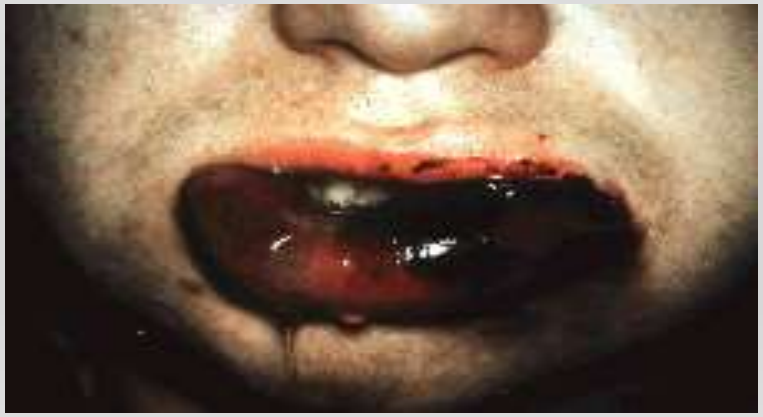
Bleeding hemophilia



Clinical Severity of Bleeding Disorders







Factor replacement

- 1 u/kg raises FVIII levels 2%

  1/2 life : 12 hrs

- 1 u/kg raises FIX levels 1 %

  1/2 life 20-24 hrs

Minor Bleeding Episodes

- Early joint bleeds
- Soft tissue & muscle bleeds
- Nose & gum bleeding not responding to local measures
- Treatment of minor bleeding episodes
  - 40 - 50% correction
  - FVIII : 25 units / kg
  - FIX : 50 units / kg

Major Bleeding Episodes

- Advanced soft tissue & muscle bleeds
- Head & neck injuries
- Gastrointestinal bleeding
- Advanced joint bleeding
- Treatment of major bleeding episodes
  - 80 – 100 % correction
  - FVIII : 50 units / kg
  - FIX : 100 units / kg

ITP

- Usually acute onset; immune mediated; post viral
- Peak 2-5 years of age, males=females
- Spontaneous bruises, petechiae
- PE –no lymphadenopathy (LN), hepatosplenomegaly.
- CBC- other cell lines normal, large platelets on smear
- Treat if platelet < 20,000 or wet ITP, avoid NSAIDS, Aspirin.
- Treat- IVIG best response, 48-72 hours; Side effects.
  - Anti-D (WInRho) Rh+ ,hemolysis, quick response
  - Steroids good response, inexpensive, need BM
- BM- Increased megakaryocytes, otherwise normal

TABLE 14.8 Characteristics of ICH in ITP

Incidence	0.2–0.8%
Age	13 months–16 years
Platelet count	<20,000 in 90% of cases
	<10,000 in 75% of cases
Interval between diagnosis of ITP and ICH	At presentation (25% of cases)
	<1 week (45% of cases)
	1 week–6 months (25% of cases)
	>6 months (30%)

Identifiable risk factors for ICH include:

- Head injuries (33%) (vs 1% in ITP without ICH)
- Hematuria (22%) (vs 0% in ITP without ICH)
- Hemorrhage more than petechiae and bruises (63%) (vs 44% in ITP without ICH)
- Arteriovenous malformation
- Aspirin treatment

Site of ICH

- Intracerebral (77% of cases)—87% supratentorial; 13% posterior fossa
- Subdural hematoma (23% of cases)

Prior treatment

- 70% had prior treatment

Survival

- 75% survive, but 1/3 have neurologic sequelae

Corticosteroids

Prednisone 1–2 mg/kg/day in divided doses orally for 2–4 weeks with tapering after there is a platelet response. The initial response rate is 50–90% (children tend to be at the higher end of the response range). Another approach is to use 4 mg/kg/day of prednisone for a short period of time with rapid taper (total dosing period of 7–14 days). As with any initial therapy of newly diagnosed ITP, many children go into sustained remission after a single course.

Dexamethasone in a daily dose of 40 mg/kg/day (24 mg/m^2) orally for 4 days given every 14 days for three cycles has been shown to have an initial response rate of 85% in adults and children but durable response is not nearly as good.

Prolonged use of steroids in ITP is undesirable. Large doses or prolonged usage may perpetuate the thrombocytopenia and depress platelet production. It also leads to side effects including gastritis, ulcers, weight gain, cushingoid facies, fluid retention, acne, hyperglycemia, hypertension, mood swings, pseudotumor cerebri, cataracts, growth retardation, and avascular necrosis.

Mechanism of action of steroids:

- Inhibit the phagocytosis of antibody-coated platelets.
- Inhibit platelet antibody production.
- Suppress activation of T-cells driving the autoimmune response.

Immune Globulin (IVIG)

Immune Globulin (IVIG) can be administered in a dose of 0.4–1 g/kg/day for 1–5 days for initial therapy or for relapsed disease. IVIG is preferred over steroids in children less than 2 years of age because they tend to have lower response rate to steroids and more challenging behavioral risk factors for bleeding.

Meta-analysis of randomized controlled trials has shown a more rapid response to IVIG in children compared to corticosteroids. In addition, a large, retrospective study has suggested that there may be a lower rate of chronic disease in patients initially treated with IVIG compared to those treated with prednisone. However, IVIG as an alternative therapy to corticosteroid therapy is much more expensive and has significant side effects (see below).

Mechanism of action of IVIG

Early studies suggested that IVIG inhibits clearance of Ig-coated platelets. Recent studies of mouse models of ITP suggested the hypothesis that IVIG upregulates FcγRIIb, the inhibitor of FcγR, on phagocytes.

Adverse effects of IVIG

- Post-infusion headache in >50% of patients. It is transient but occasionally severe (in severe cases, administer IV steroids, e.g., dexamethasone 0.15–0.3 mg/kg IV). Severe headache in ITP may suggest the presence of intracranial hemorrhage and, if clinically indicated, may require a CT scan, although most post-IVIG headaches occur with good platelet counts. Amelioration of this adverse effect with

Anti-D Therapy

IV anti-D is used in a dose of 50–75 μg/kg for initial therapy or for recurrent disease. Approximately 70% of patients have an initial response to 75 μg/kg of anti-D therapy within 1 day (comparable to high-dose IVIG). The effect is more pronounced after 48–72 h. Anti-D is plasma-derived, immune globulin with high titers against the Rhesus D antigen. It can be used only in Rh+ (and in DAT-negative and non-anemic) patients for the treatment of ITP. Hemolysis is expected when anti-D is used, and hemoglobin levels usually decrease by 0.5–2 g/dl.

Mechanism of action

Anti-D works by binding to Rhesus D antigen expressed on red blood cells, which leads to their recognition by Fc receptors on cells of the reticuloendothelial system. The coated red cells slow clearance of antiplatelet antibody-coated platelets.

Adverse effects (largely preventable by premedication with high-dose steroids)

- Fever and chills.
- Intravascular hemolysis.
- Headache, vomiting.
- Anaphylaxis (rare).

Treatment

A number of treatment options exist (Table 511.3), but there are no data showing that treatment affects either short- or long-term clinical outcome of ITP. Many patients with new-onset ITP have mild symptoms, with findings limited to petechiae and purpura on the skin, despite severe thrombocytopenia. Compared with untreated controls, treatment appears to be capable of inducing a more rapid rise in platelet count to the theoretically safe level of >20 × 10^9/L, although no data indicate that early therapy prevents ICH. Antiplatelet antibodies bind to transfused platelets as well as they do to autologous platelets. Thus, platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present. Initial approaches to the management of ITP include the following:

1. No therapy other than education and counseling of the family and patient for patients with minimal, mild, and moderate symptoms, as defined earlier. This approach emphasizes the usually benign nature of ITP and avoids the therapeutic roller coaster that ensues once interventional therapy is begun. This approach is much less costly, and side effects are minimal. Observation is recommended by the American Society of Hematology guidelines for children with *only* mild bleeding symptoms such as bruising or petechiae.

2. Treatment with either IVIG or corticosteroids, particularly for children who present with *mucocutaneous* bleeding. As American Society of Hematology guidelines state, "A single dose of IVIG [intravenous immune globulin] (0.8-1.0 g/kg) or a short course of corticosteroids should be used as first-line treatment." IVIG at a dose of 0.8-1.0 g/kg/day for 1-2 days induces a rapid rise in platelet count (usually >20 × 10^9/L) in 95% of patients within 48 hr. IVIG appears to induce a response by downregulating Fc-mediated phagocytosis of antibody-coated platelets. IVIG therapy is both expensive and time-consuming to administer. Additionally, after infusion, there is a high frequency of headaches and vomiting, suggestive of IVIG-induced aseptic meningitis.

3. Corticosteroid therapy has been used for many years to treat acute and chronic ITP in adults and children. Doses of prednisone at 1-4 mg/kg/24 hr appear to induce a more rapid rise in platelet count than in untreated patients with ITP. Corticosteroid therapy is usually continued for short course until a rise in platelet count to >20 × 10^9/L has been achieved to avoid the long-term side effects of corticosteroid therapy, especially growth failure, diabetes mellitus, and osteoporosis.

Emergency Therapy

Patients with profound mucosal bleeding or internal bleeding require immediate therapy. Combination therapy is optimal:

- IV methylprednisolone 30 mg/kg/day for 1–3 days.
- IVIG 1 g/kg/day for 2–3 days with or without:
  - Anti-D 75 µg/kg (one dose).
- Platelet transfusion (bolus followed by continuous infusion if required).
- Recombinant human factor VIIa (rhuVIIa).
- Emergency splenectomy in urgent, life-threatening bleeding is not usually recommended but can be pursued.

DIC

- **consumption of clotting factors, platelets, and anticoagulant proteins.**

- **Consequences of this process include**

  widespread intravascular deposition of fibrin, leading to tissue ischemia and necrosis, a generalized hemorrhagic state, and

  hemolytic anemia

CLINICAL MANIFESTATIONS

- accompanies a severe systemic disease process
- Bleeding first occurs from sites of venipuncture
  - or surgical incision
- The skin may show petechiae and ecchymoses.
- Tissue necrosis may involve many organs and can be most spectacularly seen as infarction of large areas of skin, subcutaneous tissue, kidneys
- Anemia caused by hemolysis may develop rapidly, owing to microangiopathic hemolytic anemia

LABORATORY FINDINGS

- Decrease certain coagulation factors (factors II, V, and VIII, and fibrinogen) and platelets
- Prolonged PT,PTT,TT
- Fragmented and schistocyte in PBS
- fibrinogen degradation products (FDPs, D-dimers) appear in the blood

Sickle cell emergency

- Fever
- Stroke
- Splenic sequestration
- Acute chest syndrom

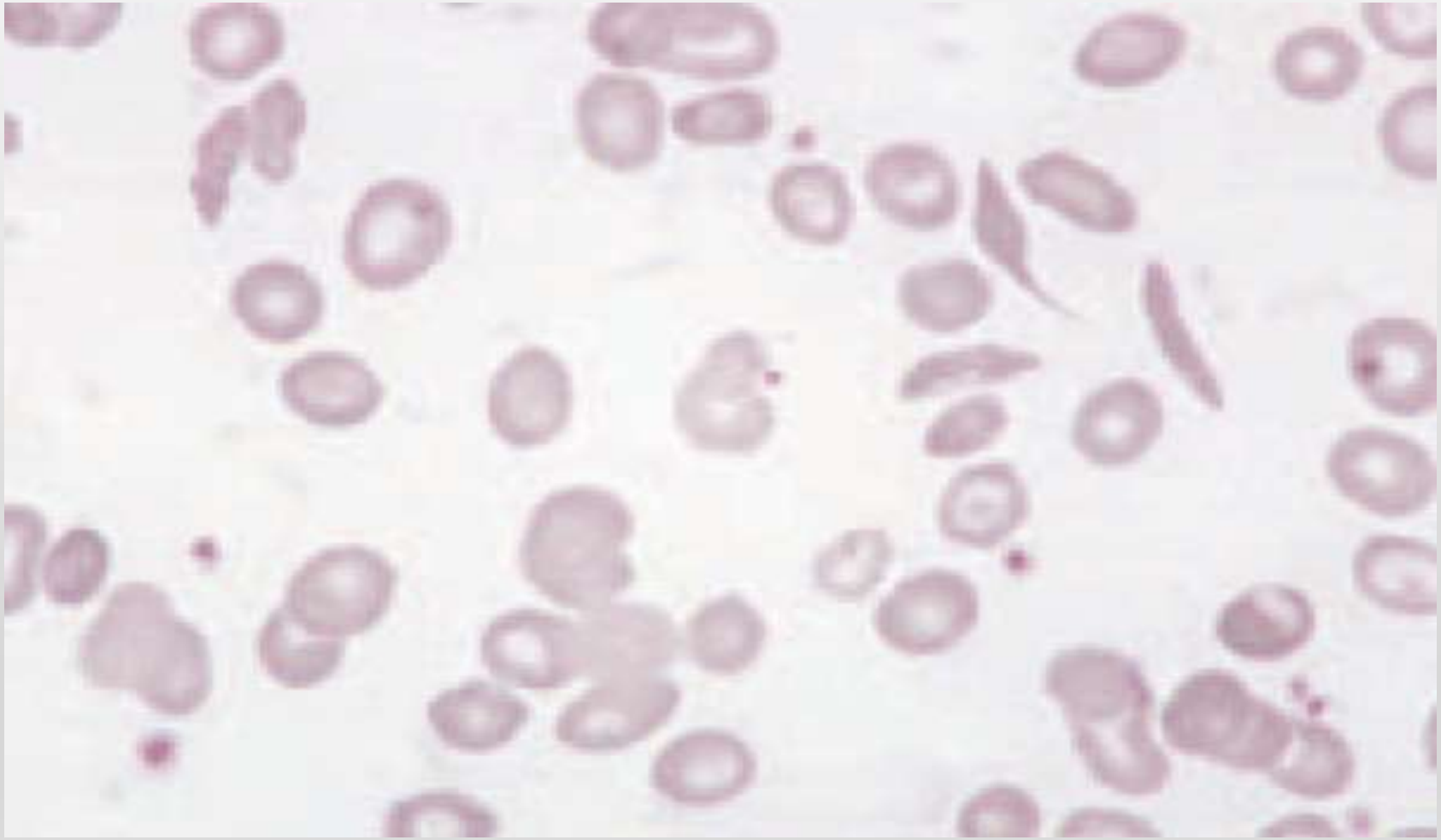
GENETIC

- **βS mutation results in an abnormal β globin with valine substitution for glutamic acid at the sixth position**

- **NL Hb in peaple > 6 mo :**
- **Nl genotype β/β**

* Hb A: $\alpha_2\beta_2$ 97%
* Hb A_2: $\alpha_2\delta_2$ 2-3.5%
* Hb F: $\alpha_2\gamma_2$ 1%

- **In SICKLE : Hb S : β/β^s (sickle trait) OR β^s/β^s (sickle cell anemia)**



CLINICAL MANIFESTATIONS

- extremely variable
- Some patients are asymptomatic
- others suffer often from acute painful episodes

❑ **Acute Sickle Cell Crises:**

- The term sickle cell crisis: “any new syndrome that develops rapidly in patients with SCD

➢ **three categories of sickle crisis:**

- vaso-occlusive
- Sequestration
- aplastic

Vaso-occlusive crises

- painful episodes resulting from intravascular sickling and tissue infarction
- occur most commonly in the bones, soft tissues, lungs, liver, spleen, brain, and penis
- may be precipitated by physical stress, infection, dehydration, hypoxia, local or systemic acidosis, exposure to cold, changes in climate, psychological factors and swimming for prolonged periods

Acute Painful Crisis

- rapid onset of deep pain, sometimes accompanied by local tenderness, erythema, warmth, and swelling
- The underlying pathology is bone marrow ischemia, with acute inflammatory infltrate
- The most commonly involved areas are the lumbosacral spine, knee, shoulder, elbow, and femur
- joint effusions during acute periarticular episodes are particularly common in the knees and elbows
- Even in patients with measurable signs of inflammation, the diagnosis of infarction is favored over osteomyelitis
- Acute long-bone infarction is at least 50 times more common than osteomyelitis

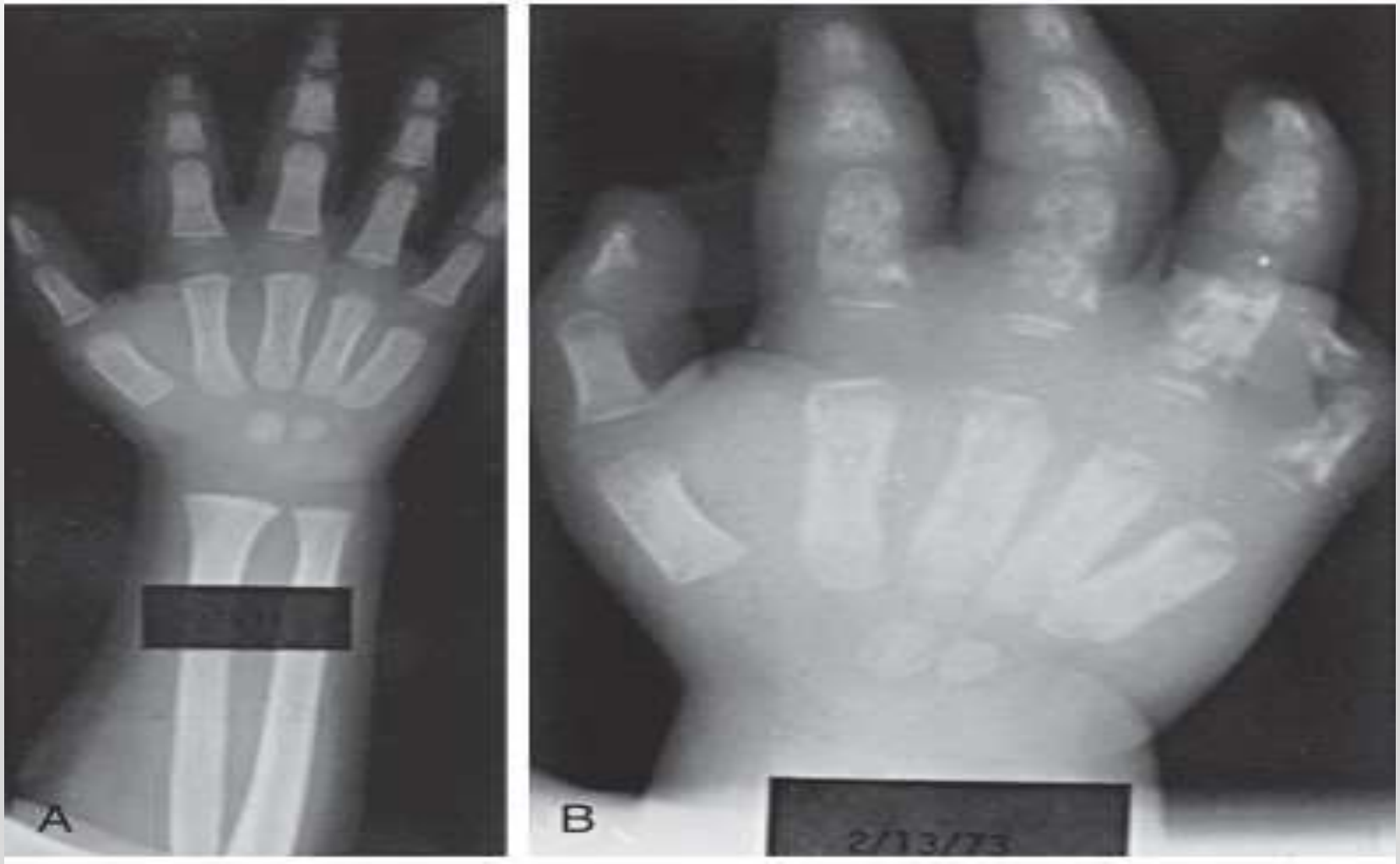
Acute Painful Crisis

- **The most common organism causing osteomyelitis is Salmonella though Staphylococcus, S. pneumoniae and Gram-negative enteric bacilli are also common**

❑ **Dactylitis: hand-foot syndrome, is ofen the frst manifestation of pain in infants and young children**

➢ **occurring in 50% of children by their 2nd yr of life**

➢ **symmetric or unilateral swelling of the hands and/or feet**


A
B
2/13/73

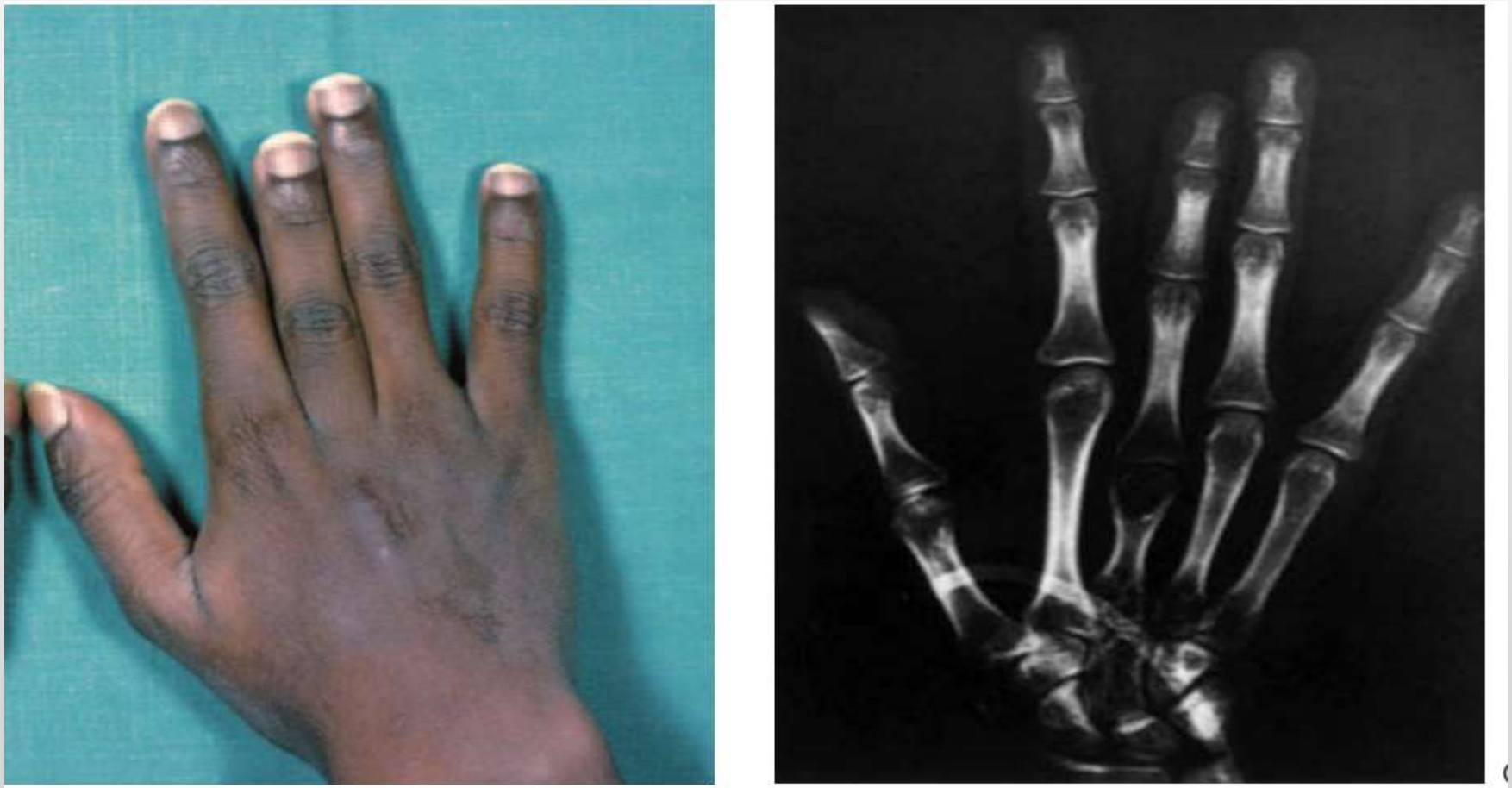


Fig. 4.8 Long-term result of 'dactylitis' in sickle cell anaemia: (a) the hand of an 18-year-old Nigerian man; (b) X-ray of the hand. (Reproduced from Hoffbrand AV and Pettit JE. *Essential Haematology*, 3rd edn. Blackwell Scientific Publications, Oxford, 1993, by kind permission of Professor A. V. Hoffbrand.)

Management of Vaso-Occlusive Pain Episodes

At home

NSAID and/or acetaminophen

If continued pain, add oral opiod

Mild pain—codeine

Moderate pain—oxycodone, hydrocodone, morphine

Supportive measures: Heating pad, Fluids

Stool softeners and/or laxative if taking opiods for more than 12 days

If pain persists or worsens, patient should be evaluated and treated in an acute care setting

In Emergency Department/Acute Care Unit

If no pain medications were taken prior to arrival and pain not severe, may use NSAID and oral opioid

If prior pain medications were taken or pain is severe: Ketorolac, IV opioid

Fluids to maintain euvolemia. IV normal saline bolus should only be used if evidence of decreased oral intake/dehydrat

Management of Vaso-Occlusive Pain Episodes

Inpatient

Continue IV opioids. Should be given as scheduled medication rather than "as needed"

Consider patient-controlled analgesia pump if pain not adequately controlled

Supportive care:

Fluids (oral IV) to maintain euvolemia

Incentive spirometry

Heating pad—must be used carefully to avoid burns

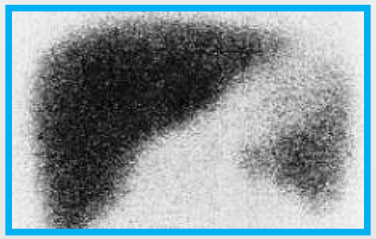
Bowel regimen to prevent/treat constipation secondary to opioid use, Stool softeners

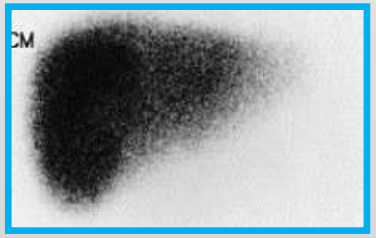
Laxative (e.g., senna)

Transition to oral nonsteroidal and oral opiod as pain level improves

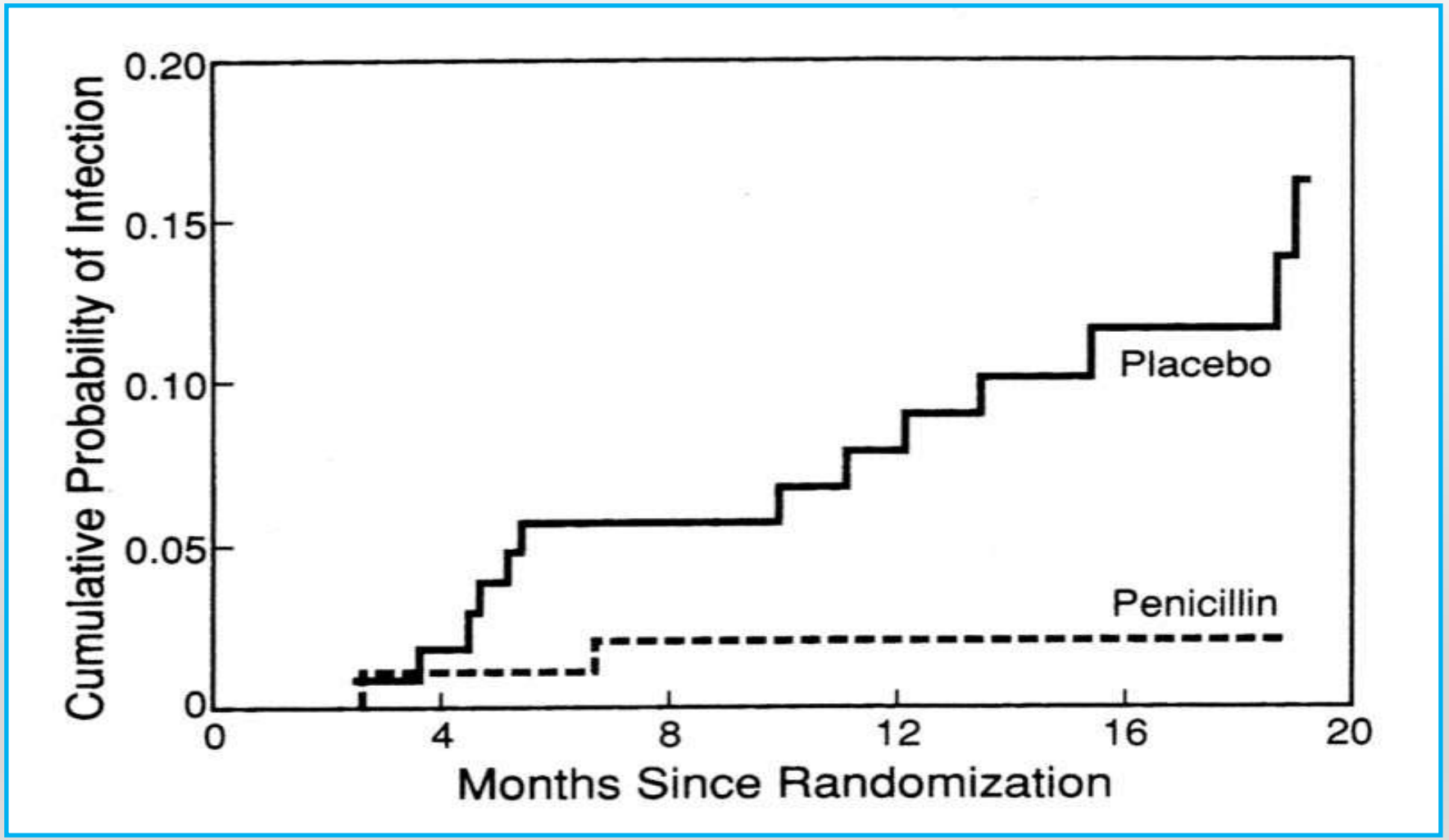
Bacteremia and Sepsis

- Functional asplenia develops after repeated splenic infarctions
- Leads to an increased risk of sepsis, particularly with *Streptococcus pneumoniae.*
- Prior to PPV 23, the risk of pneumococcal disease was 10% in children < 5years of age.
- 300 times greater than the general population.





Risk of pneumococcal sepsis in infant SCA Prophylaxis



Management of Fever

- Fever is an emergency!

- Do not use antipyretics for fever at home .

- If temp >100.4 F (38.0 C) → ER visit .

- Basic labs: CBC,ESR,CRP, U/A, UC,BC, CXR .

- Empiric IV antibiotics (e.g., ceftriaxone 75 mg/kg) .
- Observe for 3 hours .
- Follow up in 24 hours
  - Give second IV antibiotic dose in 24 hours.

- Admit if: toxic appearing, hemodynamic instability, WBC >30,000/µL or <5,000/µL, prior history of sepsis, temp > 40 C, social concerns .
- Consider adding vancomycin if any of the above .

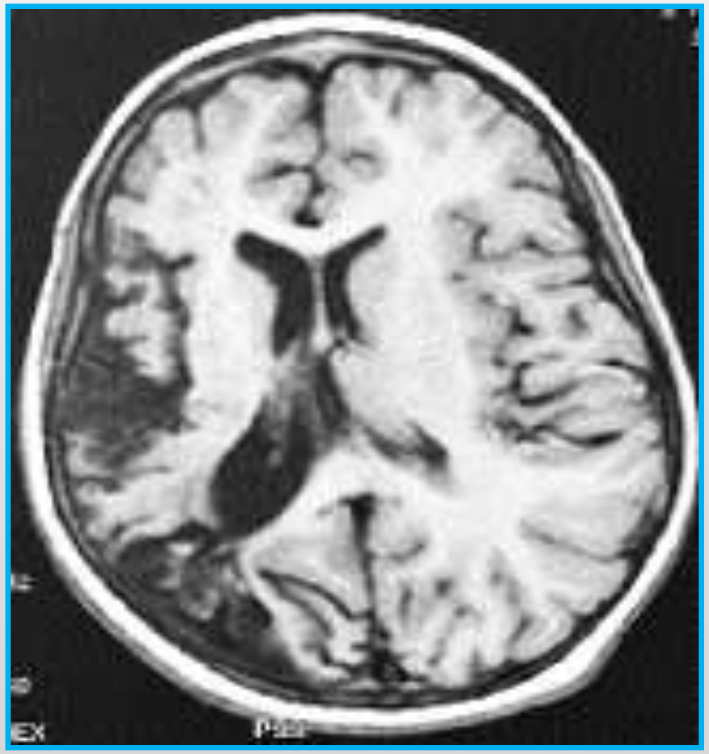
Many centers recommend inpatient hospitalization for all children younger than 5 years because this group is at highest risk of infection. In addition, all children, regardless of age, with the following high-risk features should be admitted:

- Ill appearance.
- High fever (>39.5°C).
- ACS.
- Meningeal signs.
- Enlarging spleen
- Elevated leukocyte count (>30,000/mm3).
- Falling blood counts or low reticulocyte count.

A subset of lower-risk children, over age 12 months and without the above high-risk features, may be considered for discharge after a shorter period of observation (4–18 h) after having received a long-acting antibiotic such as ceftriaxone. This option should only be considered if the family can be contacted readily, follow-up is ensured, and continuous blood culture monitoring is available.

Stroke in SCD

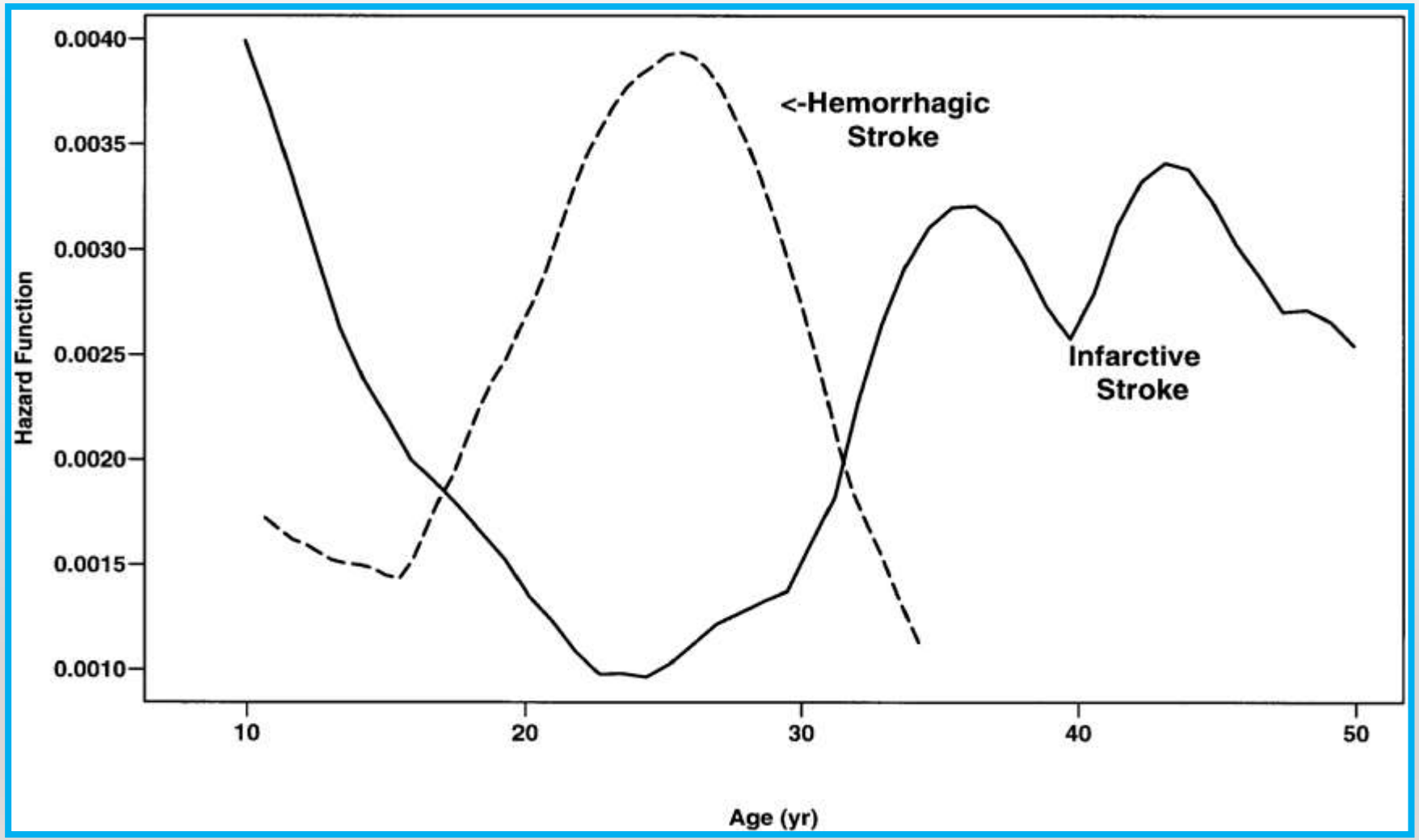
- Occurs in 5 – 10% of children with HbSS
- Thrombotic or infarctive event involving large intracranial arteries
- Presents with weakness, aphasia, seizures, LOC
- Often results in permanent neurological damage and long-term disability



Overt stroke

- Acute symptomatic stroke is **usually infarctive** in children, although **hemorrhagic** stroke may occur, particularly in older children and adults
- The most common underlying lesion is **intracranial arterial stenosis or occlusion**, usually involving the large arteries of the circle of Willis, particularly the distal internal carotid artery (ICA) and the middle (MCA) and anterior cerebral arteries (ACAs)
- **Chronic injury** to the endothelium of vessels by sickled RBC results in **changes in the intima** with proliferation of fibroblasts and smooth muscle
- the lumen is **narrowed** or completely obliterated

Rates of Stroke in HbSS by



STROKE

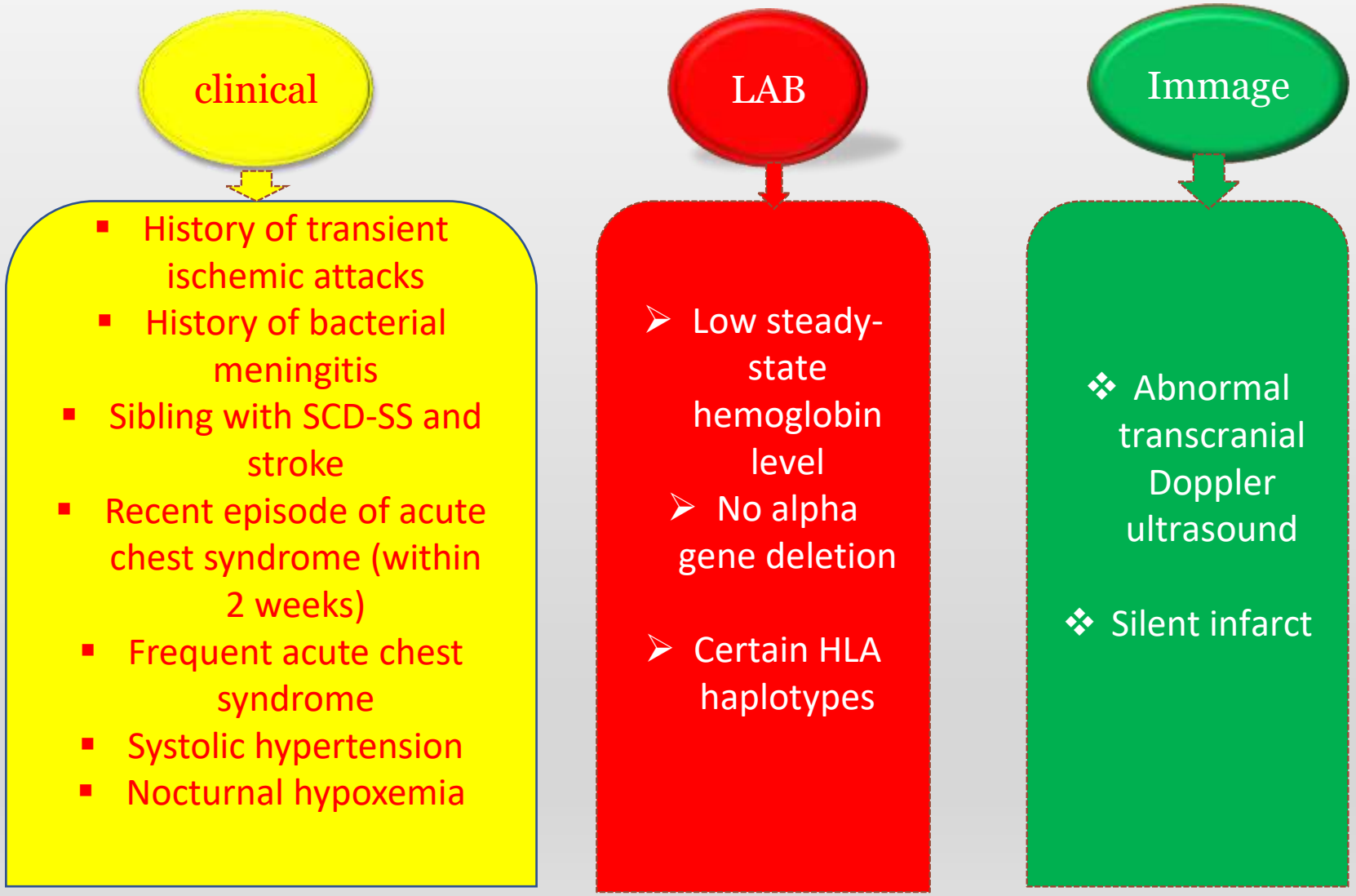
- Can be ischemic (younger) or hemorrhagic (older) .

  - Administer oxygen and IV fluids .
  - CBC & retic, Type and cross .
  - CT Scan brain .
  - Alert Blood bank - exchange transfusion .

Overt stroke

- Infarction of brain tissue occurs acutely as a result of in situ occlusion of the damaged vessel or distal embolization of a thrombus
- Stroke is most common in homozygous SCD-SS
- Prior to transcranial Doppler (TCD) ultrasound screening with transfusions for high-risk children, stroke prevalence in children with SCD-SS was estimated at 11%, with the highest incidence rates occurring in the first decade of life

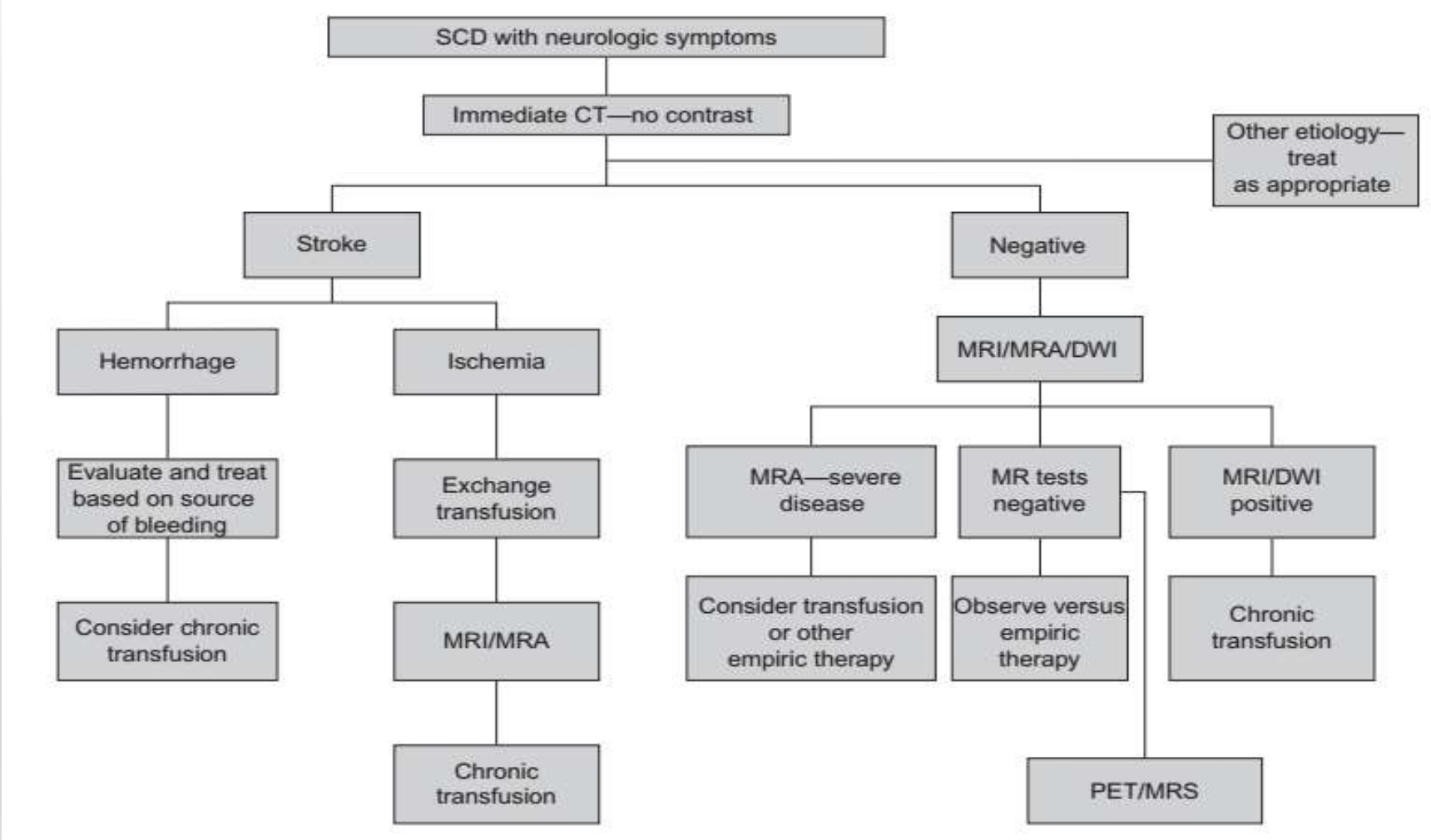
Factors Associated with Increased Risk of Overt Infarctive Stroke



Diagnosis of Overt stroke

Physical examination with detailed neurological examination
Head CT scan is useful for detecting intracranial hemorrhage and often more readily available than magnetic resonance imaging (MRI). May not be positive for acute infarction within the first 6 h
Brain MRI is more sensitive to early ischemic changes and may be
abnormal within 1 h., but should not delay empiric treatment
Magnetic resonance arterial angiography (MRA)—demonstrates large-vessel disease

Management of the child with neurological symptoms



Treatment of Overt stroke

Exchange transfusion, should be performed as soon as possible

The goal is to reduce the amount of HbS to less than 30% and to raise the hemoglobin level to approximately 10 g/dl

If exchange transfusion is not readily available, a simple transfusion to raise the hemoglobin level to no greater than 10 g/dl

Supportive therapy including avoiding hypotension and maintaining adequate oxygenation and euthermia should be initiated as adjunctive therapy

Prevention of recurrent stroke

- A chronic red cell transfusion program should be instituted, with the goal of maintaining the pretransfusion HbS level at less than 30%
- After a period of 3-4 years after the initial stroke, it may be possible to allow the pretransfusion HbS level to rise to less than 50% in low-risk patients
- Hematopoietic stem cell transplantation (HSCT)

➢ **Treatment with HU :**

- with a several month overlap period with transfusions
- was associated with a stroke recurrence rate of 3.6 events per 100 patient years, which is lower than the risk of stroke recurrence without treatment
- Prophylactic aspirin may also be useful in children with progressive vasculopathy, but the risks of hemorrhage must be weighed against the potential benefit

Primary stroke prevention

- **TCD** ultrasonography is a noninvasive study used to measure the blood flow velocity in the large intracranial vessels of the circle of Willis
- Elevated velocity in the ACA is associated with increased stroke risk
- Chronic transfusion should be instituted for children with ACA **velocity >200 cm/s**, and any child if silent infarcts and/or cerebral blood vessel stenosis are present on MRI/A
- TCD screening is recommended for children with SCD-SS or SCD-Sβ0-thalassemia ages 2-16 years
- Brain MRI/MRA should be obtained in children with abnormal TCD and should be considered for children with conditional TCD
- Brain MRA is helpful to evaluate cerebral vasculature in children with repeatedly inadequate TCD or with very low velocity

TABLE 11.7 Transcranial Doppler Ultrasonography Screening Protocol

Last TCD result (TAMMvel in ICA/MCA)	Screening interval
Normal (<170 cm/s)	Annual
Low conditional (170–184 cm/s)	3–6 months[a]
High conditional (185–199 cm/s)	6 weeks–3 months[a]
Abnormal (200–219 cm/s)	1 week
High abnormal (220 cm/s or higher)	No confirmation needed—recommend treatment

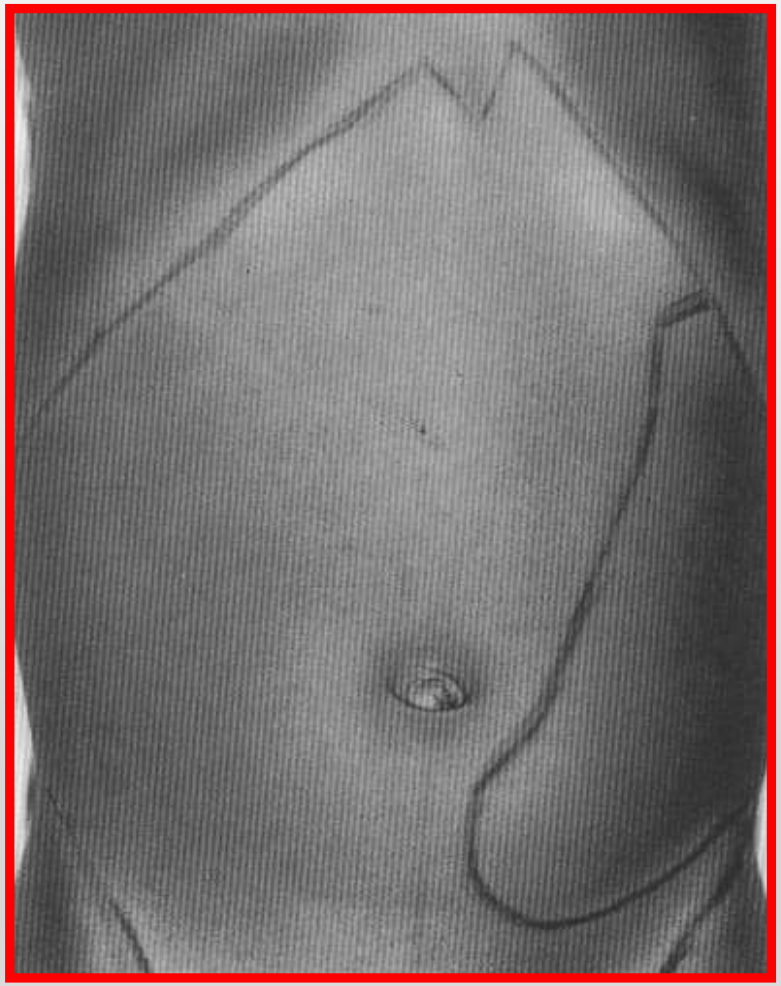
[a]*Use the shorter time interval for children <10 years old.*

- Chronic transfusion to maintain the HbS level ,30% reduces the risk of stroke by .90% in children with abnormal TCD
- Discontinuation of transfusion therapy after at least 30 months of transfusion with normalization of TCD results is associated with a high risk of reversion to abnormal TCD and stroke. Thus, transfusions are continued indefinitely
- Stem cell transplantation with an HLA-identical sibling donor should be considered
- **HU therapy** is associated with a lowering of TCD velocities and is currently under study for primary stroke prevention

Secondary Prevention of Stroke

- Without transfusion 70% recur within 3 years of initial stroke
- Chronic transfusion therapy with an aim to keep HbS<30% at all times
- Recurrence only 10% on chronic transfusion

Splenic Sequestration



Blood can pool in spleen, causing hypovolemia.

-I.V. Fluids,
-Transfuse only 5 mg/kg

Acute chest syndrome (ACS)

- 2nd most common reason for hospital admission and is associated with significant mortality
- new radiodensity on chest radiography plus any 2 of the following: fever, respiratory distress, hypoxia, cough, and chest pain
- Even in the absence of respiratory symptoms,every young children with fever should receive a CXR
- ACS is caused by infection, infarction, and/or fat embolization and iatrogenically by overhydration
- About 50% of ACS are associated with infections, including Streptococcus pneumoniae, Mycoplasma and Chlamydia, and less frequently with. Parvovirus B19 infection
- The incidence of ACS: (SS >Sβ0-thalassemia >SC > SB+THALASSEMIA), and concomitant α-thalassemia does not appear to affect ACS rates.
- higher in children with asthma
- Higher hemoglobin F levels appear to be protective

OVERALL STRATEGIES FOR THE MANAGEMENT OF ACUTE CHEST SYNDROME

- Prevention
  - Incentive spirometry in patients admitted for sickle cell pain, surgery, or febrile episodes
  - Watchful waiting in any hospitalized child or adult with sickle cell disease (pulse oximetry monitoring and frequent respiratory assessments)
  - Cautious use of intravenous fluids
- Diagnostic Testing and Laboratory Monitoring
  - Blood cultures, if febrile
  - Nasopharyngeal samples for viral culture (respiratory syncytial virus, influenza), depending on clinical setting
  - Complete blood counts every day and appropriate chemistries
  - Continuous pulse oximetry
  - CXR, for persistent or progressive illness

ACUTE CHEST SYNDROME

- **Treatment**
- **Blood transfusion (simple or exchange)**
- **Supplemental O 2 for drop in pulse oximetry by 4% over baseline, or values <90%**
- **Empirical antibiotics (third-generation cephalosporin and macrolide)**
- **Continued respiratory therapy (incentive spirometry and chest physiotherapy as necessary)**
- **Bronchodilators and corticosteroids for patients with asthma**
- **Optimum pain control and fluid management**

Prevention of ACS

- Patients with a history of recurrent ACS are candidates for preventative/curative therapies including;
- i. Hydroxyurea (HU).
- ii. Prophylactic red cell transfusions. Optimal target HbS level is not known, but usually a goal of 30-50% is used.
- iii. Stem cell transplantation.

Management of Acute Chest Syndrome

- **Antibiotics to cover pneumococcal, Mycoplasma, Chlamydia,**
- **Bronchodilator,**
- **Oxygen,**
- **Incentive spirometry,**
- **Transfusion,**
- **Steroids (controversial),**
- **NSAID's**

- **Avoid overhydration .**


THANK YOU

با تشکر از توجه شما