LEARNING OBJECTIVES

- Background Knowledge
- To Understand Pathogenesis
- How To Differentiate Between Congenital And Aquired Aplastic Anemia
- How To investigate
- Managment

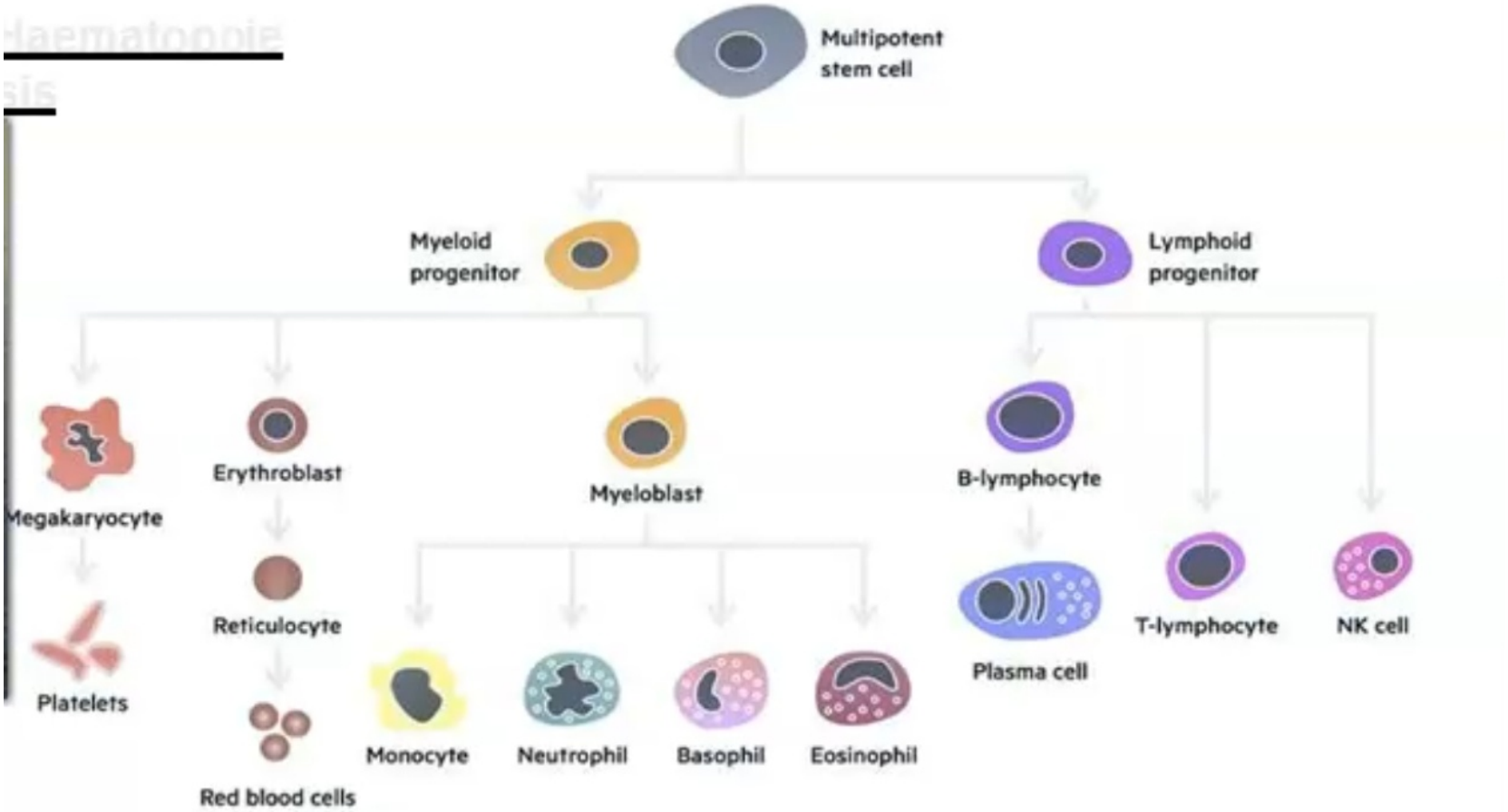
APLASTIC ANEMIA

- Disorders of the hematopoietic stem cells resulting in the suppression of one or more of erythroid, myeloid and megakaryotic cell lines.
- Two Main components
  - Hypocellular Marrow ,cellularity less Than 25%
  - Pancytopenia

- It may be inherited or acquired.

Epidemiology

- annual incidence in Europe and US - 2 cases per million population, but 4 cases in Bangkok 6 in Thailand and 14 in Japan.
- no racial predisposition exists in the United States; however, prevalence is increased in the Far East.
- The male-to-female ratio is approximately 1:1
- Aplastic anemia occurs in all age groups.
- a small peak in incidence in childhood.


Multipotent stem cell
Myeloid progenitor
Lymphoid progenitor
Megakaryocyte
Erythroblast
Myeloblast
B-lymphocyte
T-lymphocyte
NK cell
Platelets
Reticulocyte
Plasma cell
Monocyte
Neutrophil
Basophil
Eosinophil
Red blood cells

Pathogenesis

Hematopoietic stem cell may be deficient due to :

1. Acquired injury from viruses, toxins, chemicals
2. Abnormal marrow microenvironment
3. Immunological suppression(mediated by Ab or cytotoxic T cells)
4. Mutation in genes controlling hematopoiesis

TABLE .1: Etiology of aplastic anemia

A. Acquired
   a. Idiopathic
   b. Secondary
      i. Drugs, e.g. sulpha, or anticancer drugs, antiepileptics, chloromycetin, gold, etc.
      ii. Radiation
      iii. Chemicals, e.g. benzene
      iv. Viruses, e.g. Hepatitis, EBV, Parvovirus, HIV, etc.
      v. Pregnancy
      vi. Paroxysmal nocturnal hemoglobinuria (PNH)
      vii. Miscellaneous: Thymoma, eosinophilic fascitis, Hypogammaglobinemia, Preleukemic syndromes, etc.

Inherited
   a. Fanconi's anemia
   b. Dyskeratosis congenita
   c. Reticular dysgenesis
   d. Shwachman—Diamond syndrome
   e. Miscellaneous—e.g. Familial aplastic anemias, Monosomy 7, Down's syndrome, Dubowitz syndrome, Amegakaryoctic thrombocytopenic purpura, etc.

Figure 14-24 Pathophysiology of aplastic anemia. Damaged stem cells can produce progeny expressing neoantigens that evoke an autoimmune reaction, or give rise to a clonal population with reduced proliferative capacity. Either pathway could lead to marrow aplasia. See text for abbreviations.

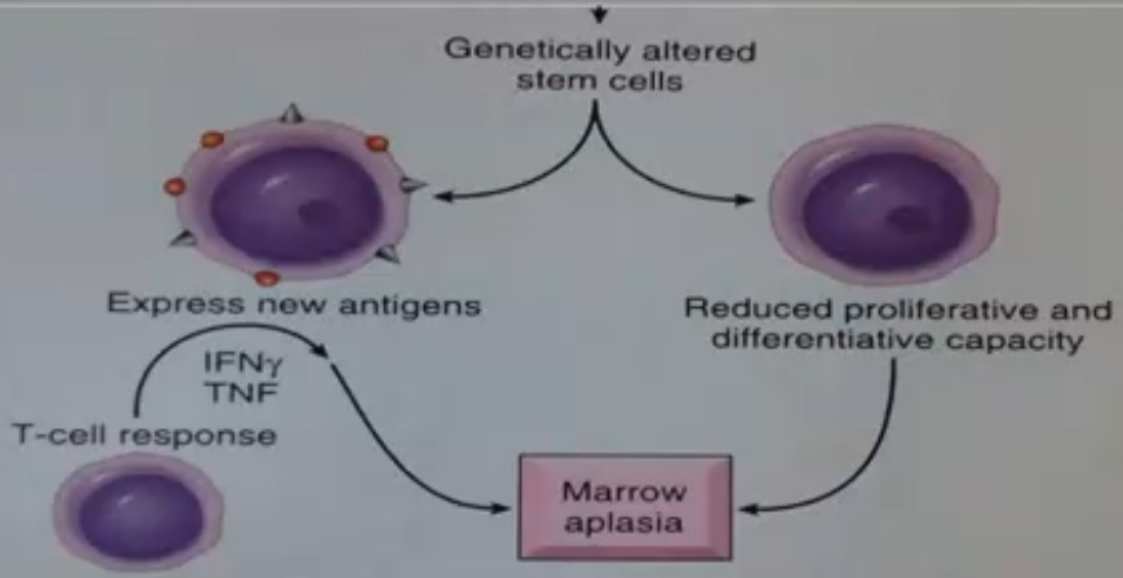


Figure 14-24 Pathophysiology of aplastic anemia. Damaged stem cells can produce progeny expressing neoantigens that evoke an autoimmune reaction, or give rise to a clonal population with reduced proliferative capacity. Either pathway could lead to marrow aplasia. See text for abbreviations.

Clinical features

- **ANEMIA**: pallor and/or signs of congestive heart failure, such as shortness of breath.
- **THROMBOCYTOPENIA**: bruising (eg, ecchymoses, petechiae) on the skin, gum bleeding, or nosebleeds.
- **NEUTROPENIA** :fever, cellulitis, pneumonia, or sepsis
- jaundice and evidence of clinical hepatitis in subset of patients

- No visceromegaly or adenopathy
- Signs of congenital aplastic anemia, look for physical stigmata of inherited marrow failure syndromes such as:
- skin pigmentation
- short stature
- microcephaly
- hypogonadism
- mental retardation
- skeletal anomalies

Investigations

- CBC
- Peripheral blood film
  Normochromic normocytic anemia in aquired disorders
  Macrocytic anemia in Fanconi anemia
- Reticulocyte count less than 1 %
- B12/folate.
- Liver function tests
- Virology (Hep B and C)
- Bone marrow aspirate & biopsy
- Serum alpha fetoproteins to R/O Fanconi's Anemia

Bone marrow exam

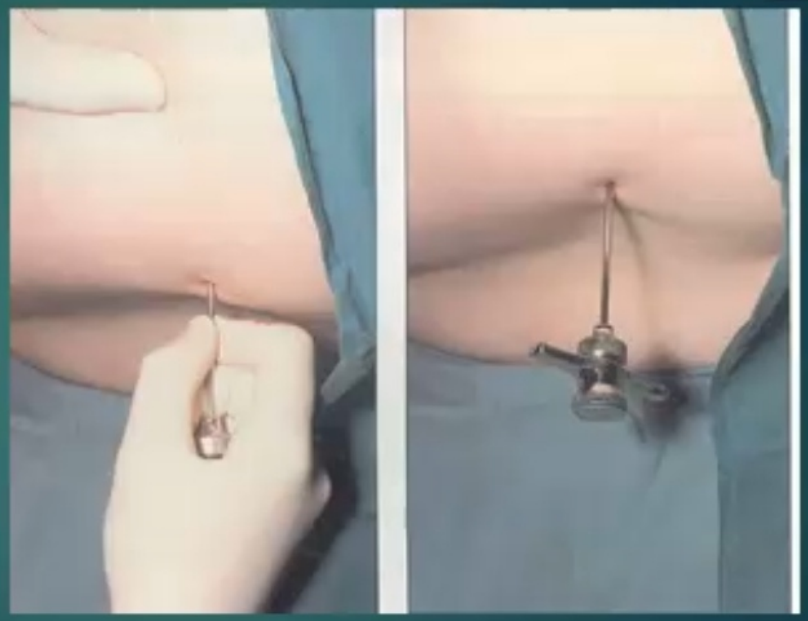
A bone marrow biopsy is performed in addition to the aspiration. In aplastic anemia, these specimens are **hypocellular.**

Only fat cells, fibrous stroma, scattered lymphocytes and plasma cells presents

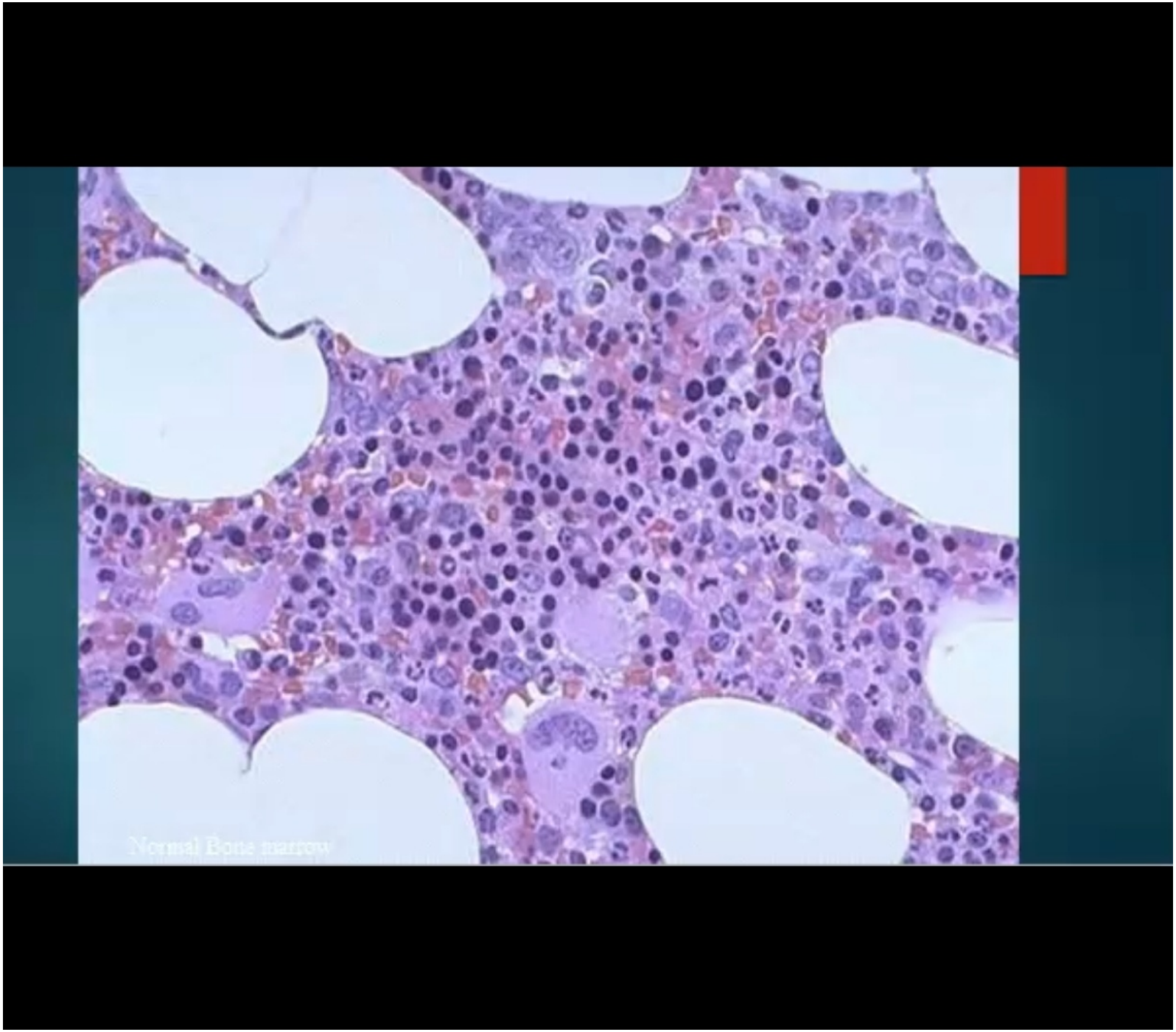
Bone marrow reveals little materials ("Dry Tap")

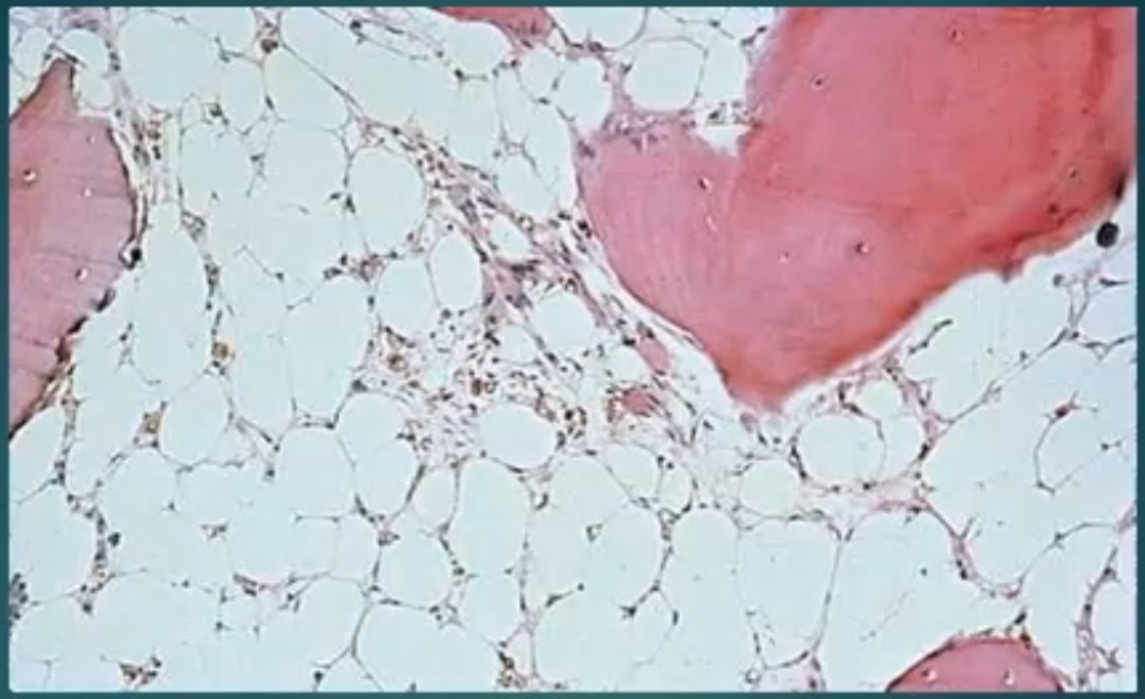
Hence biopsy is appreciated.

BM Aspiration



BM Biopsy


Normal Bone marrow



BM biopsy

hypocellular ,increased fat spaces

CLASSIFICATION

EVERE APLASTIC ANEMIA

- Absolute neutrophil count less than 500/mm3
- Platelete count less than 20,000/mm3
- Reticulocyte count less than 1 %

MODERATE APLASTIC ANEMIA

- Absolute neutrophil count between 500 and 1500/mm3
- Platelete count less than 20,000 to 1 lac/mm3
- Reticulocyte count less than 1 %

Other investigations

- Hemoglobin electrophoresis - may show elevated fetal hemoglobin.
- Biochemical profile, including evaluation of transaminases, bilirubin, lactic dehydrogenase, Coombs test, and kidney function, is useful in evaluating etiology and differential diagnosis.
- Serologic testing for hepatitis EBV, CMV, and HIV
- Histocompatibility testing should be conducted early to establish potential related donors, especially in younger patients.

Classification of AA: Camitta Criteria

Peripheral Blood Cytopenias	Non-severe (Moderate) aplastic anemia (not meeting criteria for severe disease)	Severe aplastic anemia (any 2 of 3)	Very-severe aplastic anemia (meets criteria for severe disease and absolute neutrophils < 200)
Bone marrow cellularity	< 25%	< 25%	< 25%
Absolute neutrophil count		< 500 / μl	< 200 / μl
Platelet count		< 20,000 / μl	
Reticulocyte count		< 1.0% corrected or < 60,000 / μl	

Camitta BM et al.Blood. 1976;48:63–70

Diagnosis

- Pancytopenia
- Bone marrow histology and cytology
- - decreased marrow cellularity (< 25%)
- - increased fat cells component
- - no extensive fibrosis
- - no malignancy or storage disease

- No preceding treatment with X-ray or antiproliferative drugs
- No lymphadenopathy or hepatosplenomegaly
- No deficiencies or metabolic diseases
- No evidence of extramedullary hematopoiesis

Differential Diagnosis

- Fanconi Anemia
- Dyskeratosis Congenita
- Acute Myelogenous Leukemia
- Anemia
- Aplastic Anemia
- Hairy Cell Leukemia
- Paroxysmal Nocturnal Hemoglobinuria
- Immune pancytopenias in connective tissue disorders (eg, systemic lupus erythematosus, refractory anemia)

FANCONI ANEMIA

- Most common congenital hypoplastic Anemia
- Autosomal recessive
- Presentation between 3 to 14 years
- Abnormal chromosomal breakage fragility
- All children with Microcephaly and pancytopenias should be investigated for Fanconi's

- . Females can have malformations of the vagina, uterus, and ovary.
- Many patients have a Fanconi "facies," including microcephaly, small eyes, epicanthal folds, and abnormal shape, size, or positioning of the ears
- Approximately 10% of patients are mentally retarded.
- Ectopic, pelvic, or horseshoe kidneys are detected by imaging, as well as duplicated, hypoplastic, dysplastic, or absent organs.

TABLE 468-2 -- Characteristic Physical Anomalies in Fanconi Anemia

ANOMALY	APPROXIMATE FREQUENCY (% OF PATIENTS)
Skin pigment changes	65
hort stature	60
per limb abnormalities (thumbs, hands, radii, ulnas)	50
pogonadal and genital changes (mostly male)	40
ther skeletal findings (head/face, neck, spine)	30
e/lid/epicanthal fold anomalies	25
enal malformations	25
r anomalies (external and internal), deafness	10
p, leg, foot, toe abnormalities	10
astrointestinal/cardiopulmonary malformations	10

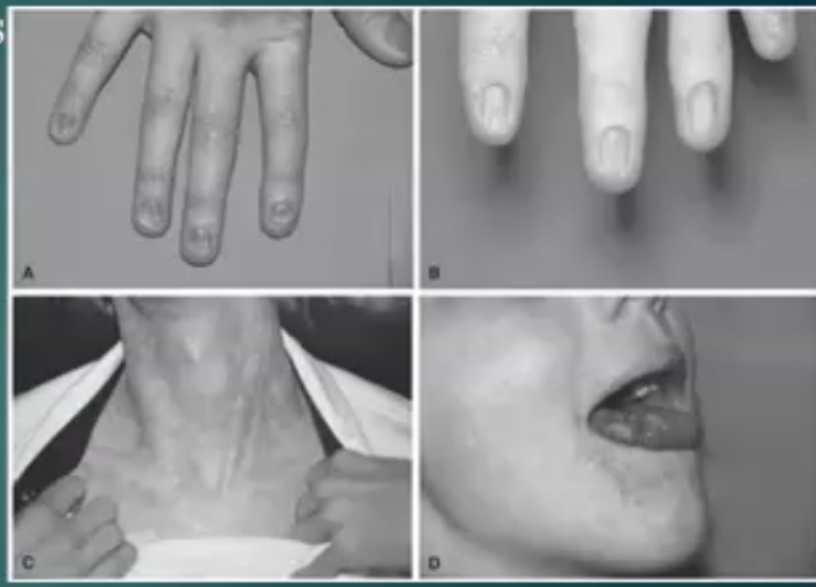
DYSKERATOSIS CONGENITA

ucocutaneous and hematopoietic systems

he diagnostic ectodermal triad is

- **Reticulate Skin Pigmentation**
- **Mucosal Leukoplakia**
- **Nail Dystrophy**

kin and nail findings usually become
parent in the 1st 10 yr of life,
hereas oral leukoplakia is seen later.



TREATMENT- APLASTIC ANEMIA

- **Supportive care**

Severe Anemia- packed red cells

Sever Thrombocytopenia- Platelets transfusion Infection- Antibiotics

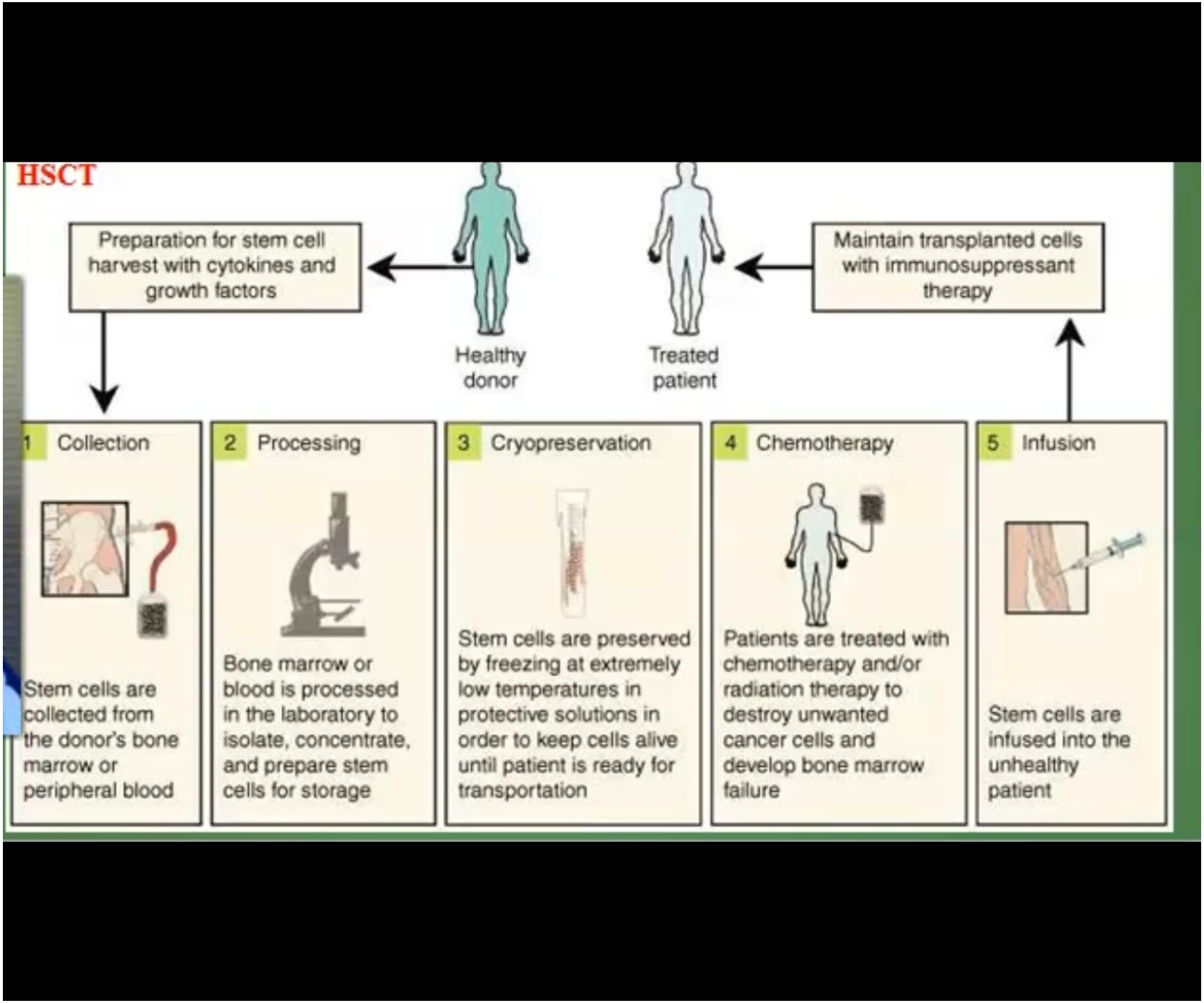
Pt. with neutropenia with infections-

A trial of granulocyte colony stimulating factor (G-CSF) or Granylocyte Macrophage colony stimulating Factor

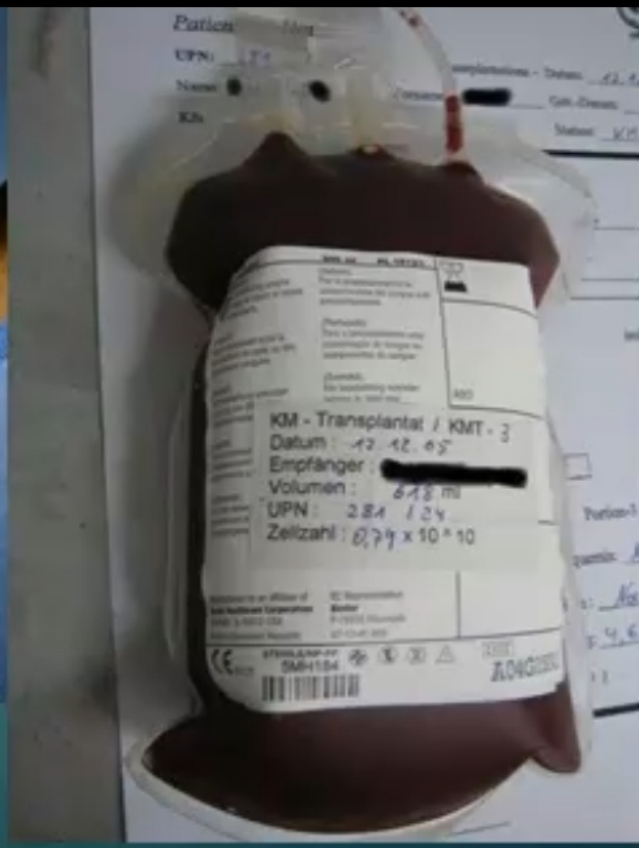
- **DEFINITIVE THERAPY**

Antithymocyte globulins and cyclosporin if no donor available

Hematopoietic stem cell transplant **(HSCT) with HLA** identical sibling marrow transplant


HSCT
Preparation for stem cell harvest with cytokines and growth factors
Healthy donor
Treated patient
Maintain transplanted cells with immunosuppressant therapy
1 Collection
Stem cells are collected from the donor's bone marrow or peripheral blood
2 Processing
Bone marrow or blood is processed in the laboratory to isolate, concentrate, and prepare stem cells for storage
3 Cryopreservation
Stem cells are preserved by freezing at extremely low temperatures in protective solutions in order to keep cells alive until patient is ready for transportation
4 Chemotherapy
Patients are treated with chemotherapy and/or radiation therapy to destroy unwanted cancer cells and develop bone marrow failure
5 Infusion
Stem cells are infused into the unhealthy patient


Harvesting


KM - Transplantat / KMT - 3
Datum : 12.12.05
Empfänger :
Volumen :
UPN : 284 124
Zellzahl : 0,79 x 10^10

PROGNOSIS

- HLA matched sibling marrow transplant 90% chance of long term survival
- Immunosuppression 60-80% survival