

Inherited Bone Marrow Failure Syndromes “IBMFS”

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Objectives of the lecture

- **Introduction to BMF and IBMFS**
- **Associated malignancies with BMFS**
- **Clinical approach to a case with suspected IBMF**
 - History (patient and family history)
 - Physical findings in different IBMFS
 - General and secfic investigations for IBMFS
- **Fanconi anemia**
 - Introduction
 - FA/BRCA repair pathway
 - Natural history of fanconi anemia
 - Clonal evolution and MDS/AML in FA patients
 - Somatic mosaicism “Natural gene therapy”
 - Management of Fanconi anemia and treatment options



Why Do We Need To Study IBMFS?

1. Hemato/oncologist is mostly the 1st to see

IBMFS may 1st present as Aplastic anemia, MDS , or even leukemia

2. Progression to some hematological and solid tumors

Early detection offers the best opportunities for cure !!

3. Need special treatment protocols and not the usual standard regimens

- ++ Morbidity and Mortality (Underlying ID, Cardiac and renal anomalies)
- RIC if HSCT is indicated

Why Do We Need To Study IBMFS?

4. HSCT

- Treats **only** the marrow disease
- Other organ system abnormalities and predisposition to solid tumors **remain**

5. Family planning

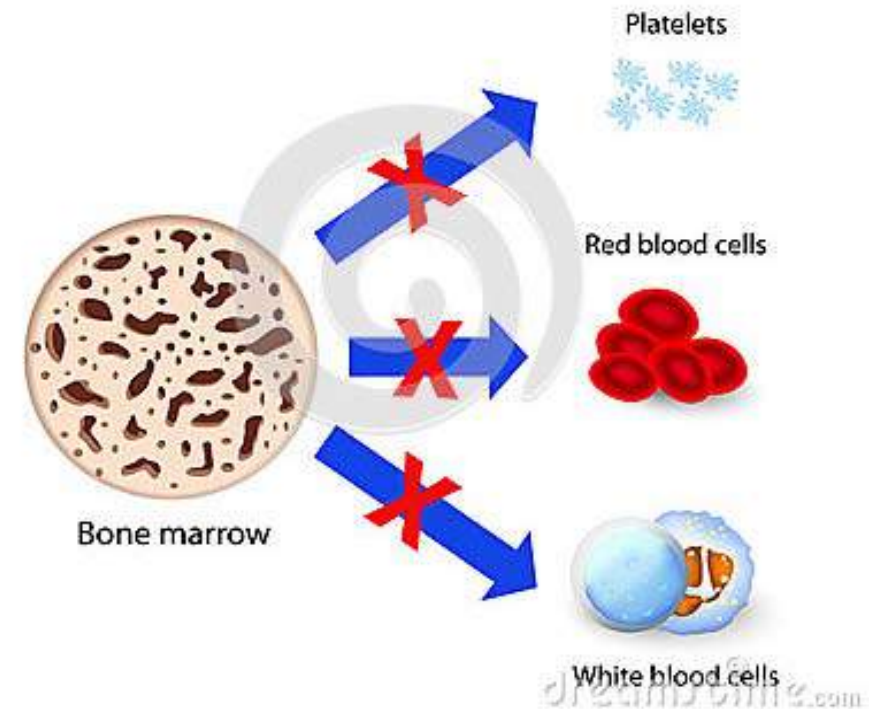
- “**Future children desired**” → prenatal testing & genetic diagnosis
- Diagnosis also **permits carrier testing** for family members seeking genetic counseling

6. Testing of siblings for IBMFS informs donor selection to avoid choosing an affected donor

What is Bone marrow failure?

- A diverse group of life-threatening blood disorders characterized by
 - Inadequate haematopoiesis
 - ± Clonal evolution
 - ± Increased risk of hematological malignancies
- BMF can be **acquired or inherited**

Aplastic anemia



CLASSIFICATION of BMF

- Acquired BMF
- **Inherited BMF** (genetic, not present at birth)
 - Pediatric disorders, but in fact, **50% are diagnosed as adults**, and ~ 60% of the cases survived to reach adulthood
 - **TAR and CAMT** are the only syndromes where the initial diagnosis is limited to children.
 - >25% of pediatric patients & ~10% of young adults who present with AA have an inherited etiology

Disorders with Hypoplastic Bone marrow

Non-hematological disorders

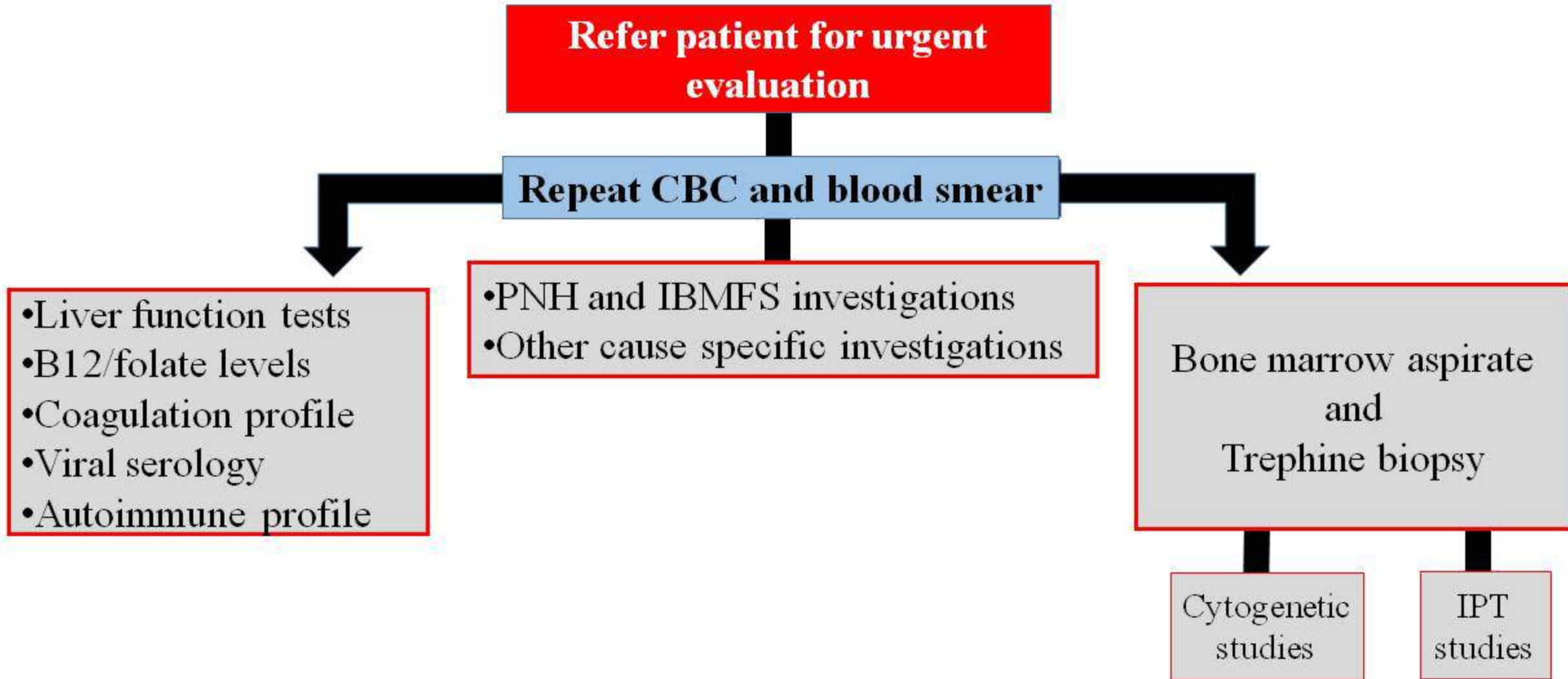
- Infections (eg, CMV, EBV, herpesvirus, parvovirus, others)
- Vitamin deficiency (vitamin B12, folate)
- Metabolic disorders (e.g. mevalonate kinase deficiency)
- Rheumatic disease
- Mitochondrial disorders (Pearson syndrome)
- ALPD (eg, fas deficiency)

Hematological disorders

- **Inherited BM failure disorders**
- Acquired Sever Aplastic anemia
- MDS (hypocellular RCC)
- Clinical PNH in the setting of BM failure
- Hypoplastic prephase of B-cell precursor ALL
- Hemophagocytic lymphohistiocytosis

Pancytopenia on **initial** CBC

Different algorithms exists



Inherited Defects of Hematopoiesis “IBMFS”

- Fanconi anemia (FA)
 - Dyskeratosis congenita (DC)
 - Congenital amegakaryocytic thrombocytopenia (CAMT)
 - Shwachman Diamond syndrome (SDS)
 - Thrombocytopenia with absent radii (TAR)
 - Diamond Blackfan anemia (DBA)
 - Severe congenital neutropenia (SCN) “Kostmann syndrome AR”
 - Single cytopenias
 - Cartilage hair hypoplasia (CHH)
 - Familial platelet disorder (FDP)
- Most frequent syndromes**
- Often develop AA and may evolve into MDS & AML
- Most rare disorders**
- Rarely if ever become aplastic but have increased risks of leukemia

Inherited Defects of Hematopoiesis “IBMFS”

- Occur at **different ages** and has highly **variable presentations**
- Underlying **pathogenesis are heterogeneous** and comprise
 - Metabolic dysfunction
 - Inhibition of differentiation
 - Ribosomal dysfunction → “**Ribosomopathies**”
 - DNA repair deficiency → “**e.g. Fanconi Anemia**”
 - Telomere maintenance → “**Telomeropathies**”
- Degree of **severity and disease kinetics** depend on

The underlying **gene mutation**

- Distinction between the **IBMFS & acquired AA** is critical to inform choice of therapy and to guide medical management
- Many of these **patients first come** to medical attention in **adulthood**
- New Molecular tests **improved ability** to diagnose but has also **created confusion** regarding their indications & interpretation

Severity of Bone Marrow Failure

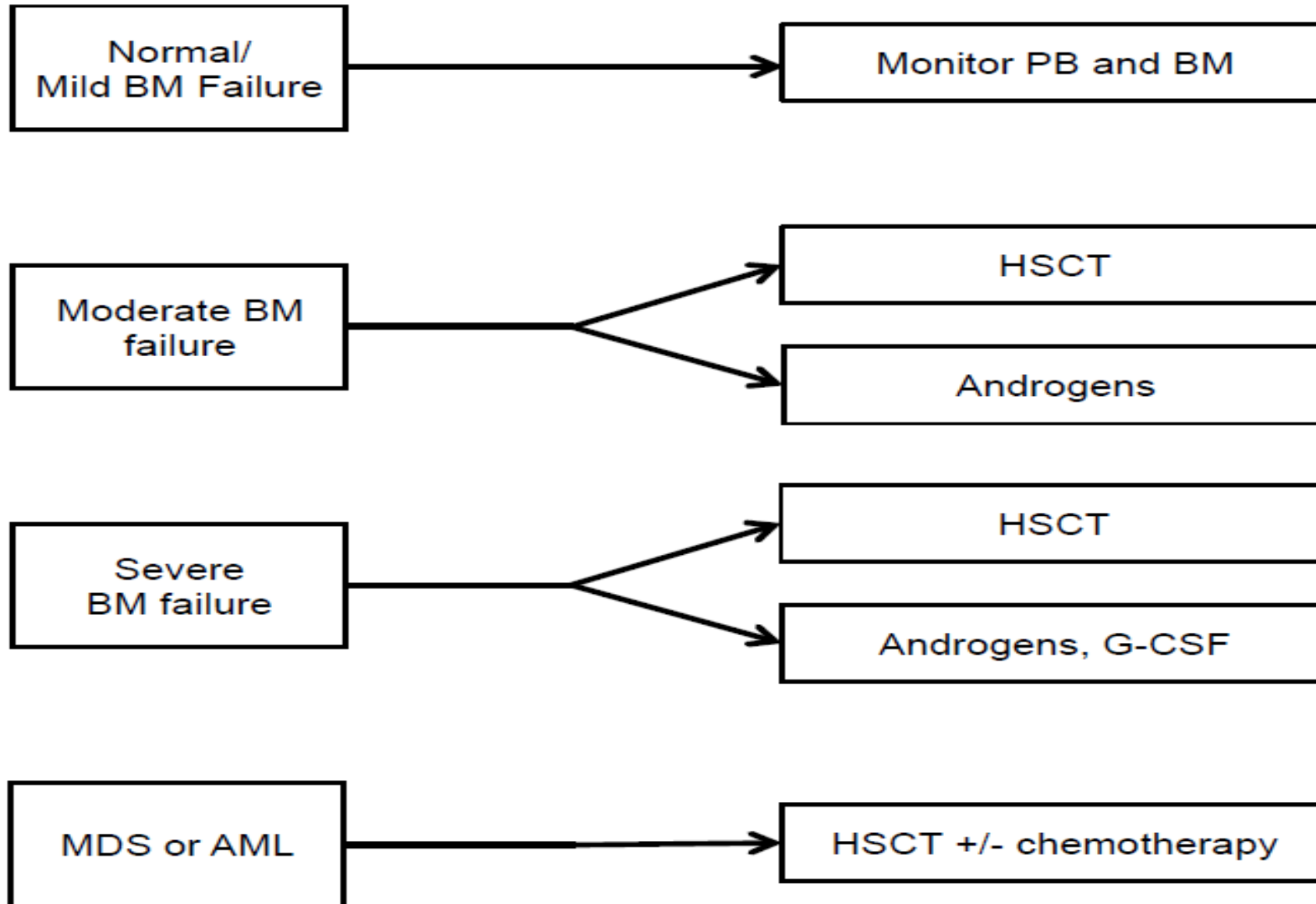
	Mild	Moderate	Severe
ANC	$<1,500/\text{mm}^3$	$<1,000/\text{mm}^3$	$<500/\text{mm}^3$
Platelets	$50,000 - 150,000/\text{mm}^3$	$<50,000/\text{mm}^3$	$<30,000/\text{mm}^3$
Hb	$\geq 8 \text{ g/dl}^*$	$<8 \text{ g/dl}$	$<8 \text{ g/dl}$

*Less than norm for age but $>8 \text{ g/dl}$

To meet these criteria for marrow failure, the cytopenias must be

1. Persistent
2. Not transient or secondary to another treatable cause
 1. Infections,
 2. Medications
 3. PB cell destruction/loss
 4. Nutritional deficiencies

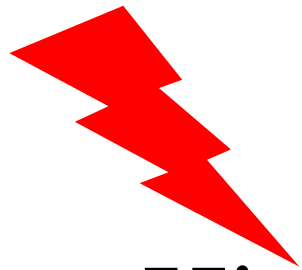
Bone marrow failure **treatment** algorithm



Susceptibility to malignancies in inherited BMFS

Inherited bone marrow failure syndrome	Reported malignancies
Fanconi anemia (FA)	MDS, AML, ALL, head and neck SCC , brain tumors, BCC, breast and skin carcinoma
Dyskeratosis congenita (DC)	MDS, AML, NHL, head and neck SCC , BCC
Diamond Blackfan anemia (DBA)	MDS, AML, colon and lung cancer , BCC, and osteogenic carcinoma
Shwachman Diamond syndrome	MDS, AML, Pancreatic ductal adenocarcinoma
Cartilage hair hypoplasia (CHH)	NHL, HD, CLL, SCC, BCC
Thrombocytopenia absent radius syndrome (TAR)	AML
Congenital amegakaryocytic thrombocytopenia (CAMT)	AML, ALL
Sever congenital neutropenia (SCN)	MDS, AML
Familial platelet disorder (FDP)	MDS, AML, MPN, acute T ALL

Approach to the patient with marrow failure



History
and
Examination

Marrow failure?

Clinical history

Family history

Examination

Laboratory

Specific investigations

Genetic mutations

Clinical approach to Marrow Failure Patient

Clinical History

- **Clues** raising suspicion for an IMFS
- Many are **non-specific** in **isolation** but warrant careful consideration in the **context** of BMF patients

Clinical approach to Marrow Failure Patient

Clinical History

1. **Birth history** (IUGR or SBW)
2. **Short** stature or failure to thrive (does not rule out)
3. **Developmental** delay or learning disabilities **#many of the IBMFS**
4. **Skin:** rash, dysmorphic nails, early hair graying **#DC** and eczema **#SDS** “exocrine dysfunction”
5. **Dental** anomalies such as dysmorphic teeth, enamel hypoplasia, or oral leukoplakia **#DC**
6. **Eye and ears:**
 1. Different anomalies **#FA and DC**
 2. Exudative retinopathy may accompany **#DC** “formerly part of Revesz \$”

Clinical approach to Marrow Failure Patient

Clinical History

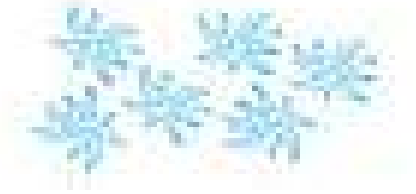
7. **GIT and hepatobiliary** manifestations
 - Fat malabsorption such as steatorrhea **#SDS** “exocrine pancreatic dysfunction”
8. **Frequent unusual infections** **#SDS & DC** “underlying immune deficiency”
9. **Pulmonary symptoms** **#DC** “2ry to restrictive pulmonary disease”
10. **Cardiac anomalies** **#FA, DC, DBA, SDS**
11. **Skeletal:** Osteopenia & pathological fractures **#many of the IBMFS**
12. **Endocrinopathies and hypogonadism** **#many of the IBMFS**

Clinical approach to Marrow Failure Patient

Clinical History

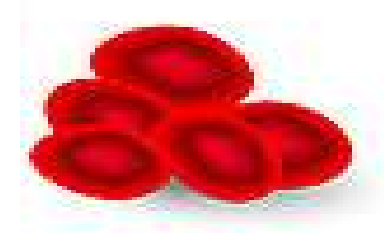
- **Congenital amegakaryocytic thrombocytopenia**
 - **#DD of the neonate with bleeding and thrombocytopenia**
 - Without any apparent cause such as
 - Infection
 - Medications
 - Maternal HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)
 - Antibody-mediated destruction

Platelets



- **Idiopathic red cell aplasia** “presenting in the first year” **#DBA**

Red blood cells



Clinical approach to Marrow Failure Patient

Family History

Important clues

- **Cancer predisposition**

- Presentation @ young age
- The spectrum of familial cancers may also be informative.

“Oral, esophageal, GI, colorectal, female genital tract cancers, AML, & lymphomas”

- Autosomal dominant pattern # **DC** or Recessive inheritance pattern # **FA**

- **Unexplained cytopenias** or **aplastic anemia**

- **Unexplained fetal loss** or **congenital anomalies**

- Diagnostic testing is recommended for **all siblings** of patients with IBMFS
- Testing of **parents** for syndromes with a dominant pattern of inheritance

Clinical approach to Marrow Failure Patient

Physical findings

Many are **non-specific** in **isolation** but warrant careful consideration in the **context** of BMF patients

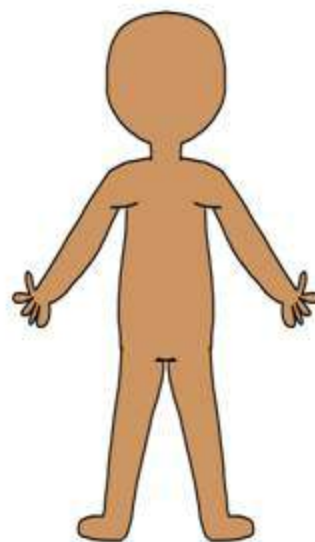
Clinical approach to Marrow Failure Patient

Facial features



- Craniofacial defects
 - Microphthalmia
 - Hypotelorism
 - Epicanthal folds
 - Broad nasal bridge
 - Cleft palate and micrognathia #DBA
- } #FA

Skin



- Skin pigmentary abnormalities #FA
“hyper- or hypopigmentation”
- Reticulated or mottled rash is #DC
- Eczematous rash #SDS
- Nail dystrophy or leukoplakia #DC

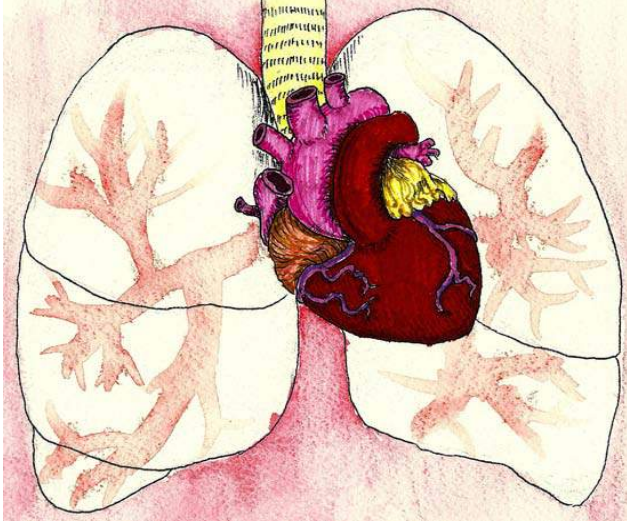
Skeletal



- Thumb anomalies and radial ray defects #FA & DBA
- Toes anomalies of the toes.
- Thoracic dystrophies #SDS
- Vertebral anomalies #FA “VATER/VACTERL \$”

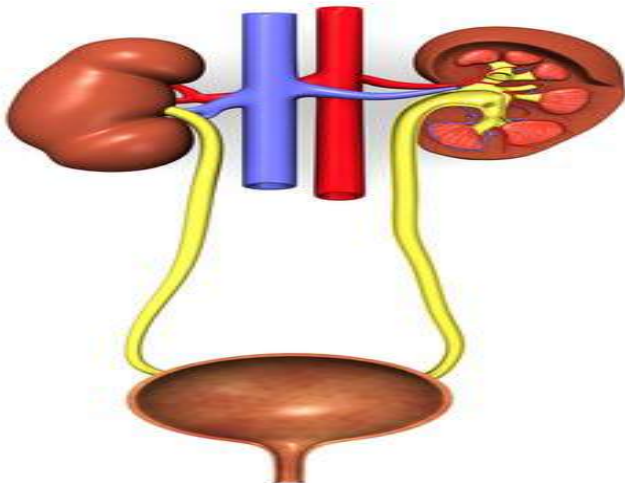
Clinical approach to Marrow Failure Patient

Cardiopulmonary



- Cardiac structural anomalies #FA, DC, DBA
- Pulmonary disease, including pulmonary fibrosis # DC

Genitourinary



- Pelvic kidney, single kidney, horseshoe kidney
- Ureteral or urethral abnormalities
- Hypogonadism, micropenis, and undescended testes

Most IBMFS

Laboratory Evaluation

Hematology

- Cytopenias “often but not exclusively” that brings the patients to the hematologist.
 - may be severe, mild, or even absent.
- Usually the **1st sign**:
 - **Pancytopenia** is the usual presentation for **FA and DC**
 - **Anemia** is the first sign in **DBA**
 - **Isolated neutropenia** may have **SCN or SDS**
 - **Thrombocytopenia** in **TAR, CAMT**
 - **AML, MDS**
- Usually the hematologic **endpoint** in
 - FA, DC, SDS, and CAMT is **AA**
 - DBA, SCN, and TAR remain **single cytopenias**
 - Evolution to leukemia (AML and/or MDS) is part of the natural history of these syndromes

Mutated genes have been identified in **all** syndromes **except TAR**, although some patients who clearly have a specific syndrome lack mutations in the known gene

Laboratory Evaluation

Hematology

- **Unexplained red cell macrocytosis**, sole hematologic abnormality particularly
 - Family history of marrow failure, cancer predisposition
 - Physical anomalies
 - Masked in patients with iron deficiency or thalassemia trait
- Elevated **hemoglobin F** levels
- **Bone marrow evaluation “no pathognomonic findings”**
 - Rule out **other disorders**, such as a malignancy
 - Follow marrow **cellularity**
 - Assess for **cytogenetic clonal** populations
 - **Dysplastic** changes
 - Micromegakaryocytes with only single or double nuclei
 - Pseudo–Pelger Huët anomalies
 - Megaloblastic features with nuclear:cytoplasmic dissynchrony
 - Multi nucleated erythroid precursors.

Laboratory Evaluation

Chromosomal Breakage Test

- Increased chromosomal breakage following exposure to clastogens such as MMC or DEB

“Gold standard for FA”

- Typically performed on PHA-stimulated peripheral blood lymphocytes “T”
- Reversion of the gene mutation in a somatic cell “typically a lymphocyte” result in a falsely negative chromosomal breakage test
- High clinical suspicion for FA but a negative blood test

The diagnosis of FA may be made by testing skin fibroblasts for chromosomal breakage

- **Genetic mutation analysis** is important to **exclude other** causes of **Chromosomal Breakage \$**
 - Ataxia telangiectasia
 - Bloom’s syndrome
 - Nijmegen breakage syndrome

Laboratory Evaluation

Telomere Length ----- Dyskeratosis congenita (DC)

- Dyskeratosis congenita (DC) is caused by **mutations in genes that affect telomere maintenance**
- Although short telomeres are commonly seen in patients with marrow failure
 - Telomere length is markedly shorter (<1st percentile) in patients with DC, even in comparison to other patients with marrow failure.
- **Granulocytes** in particular commonly exhibit shortened telomeres
- **Genetic testing for mutations** in DC genes is recommended to confirm the diagnosis
 - If **telomere length analysis is suspicious** for dyskeratosis congenita or
 - If **clinical suspicion** for dyskeratosis congenita is high
- **Unfortunately**, mutations in the DC **genes identified to date is insufficient** to rule out the diagnosis of dyskeratosis congenita, and it is likely that additional genes are involved

Laboratory Evaluation

Exocrine Pancreatic Testing --- Shwachman-Diamond syndrome (SDS)

- One of the hallmarks of SDS is exocrine pancreatic atresia **but only** a subset of patients manifest clinical symptoms.
- < 2-5% of the exocrine pancreas is required to maintain adequate digestive capacity to be clinically silent
- **Steatorrhea** resolves in 1/2 of patients with SDS presenting with this symptom
- Measurement of **serum trypsinogen** and **pancreatic isoamylase** provides a useful screen
- A **fatty pancreas on imaging studies** in a patient with marrow failure also suggests the diagnosis.
- **Fecal elastase “not been validated”** as a measure of exocrine pancreatic dysfunction in patients with SDS, it is a widely used marker in CF & a very low fecal elastase level would warrant further investigation.

Laboratory Evaluation

Exocrine Pancreatic Testing --- Shwachman-Diamond syndrome (SDS)

- **Pancreatic isoamylase**

- Normal values vary with age.
- Typically **low** before the age of 3 years even in healthy controls → best utilized in **older** patients

- **Serum trypsinogen levels**

- Often **rise** into the normal range beyond the age of 3 years even in patients with SDS → more sensitive in **younger** patients

The utility of the **both** tests is **limited**
by the lack of clinical laboratories with **clearly defined cut-off values**
distinguishing patients with SDS from healthy controls

Laboratory Evaluation

Erythrocyte Adenosine Deaminase ---- Diamond-Blackfan anemia (DBA)

- Patients with DBA often have elevated erythrocyte adenosine deaminase (eADA) levels.
- The reason for this finding is **unknown**, but this has nonetheless proven a useful diagnostic marker.

- Elevated eADA
- Fetal hemoglobin levels
- Red cell macrocytosis
- Congenital anomalies
- Familial anemia
- Age less than 1 year

Favors the diagnosis of Diamond-Blackfan anemia rather than transient erythroblastopenia of childhood (TEC)

- Laboratory testing must be interpreted cautiously during the recovery phase of TEC as some overlap with features of DBA may transiently arise.

Genetic and laboratory tests for IBMFS

Syndrome	Inheritance pattern	Gene	Additional laboratory testing
Fanconi anemia	Autosomal recessive	FANCA - FANCC FANCD1 - FANCD2 FANCE - FANCF FANCG - FANCI FANCI - FANCL FANCM - FANCN	Chromosome breakage
	X-linked recessive	FANCB	
Dyskeratosis congenita	X-linked recessive	DKC1	Telomere length
	Autosomal dominant	TERC TERT TINF2	
	Autosomal recessive	NHP2/NOLA2 NOP10/NOLA3	
SDS	Autosomal recessive	SBDS	Serum trypsinogen Pancreatic isoamylase Fecal elastase Pancreatic imaging
CAMT	Autosomal recessive	C-MPL	
Diamond-Blackfan anemia	Autosomal dominant	RPS19, RPS17, RPS24, RPL35A RPL11	Erythrocyte adenosine deaminase (ADA)

Fanconi Anemia

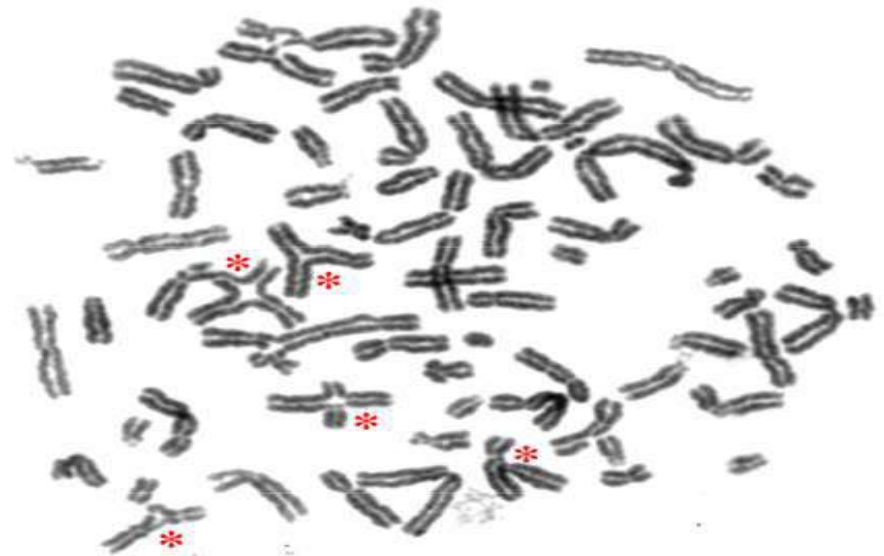
- Fanconi anemia (FA) is a rare inherited BMFS characterized by
 - Congenital and endocrine anomalies
 - Impaired hematopoiesis, and cancer predisposition.
- FA can be **clinically** and **genetically** very heterogeneous
- Guido Fanconi, a Swiss pediatrician, was the first to describe this disorder in three brothers with pancytopenia, short stature, and hypopigmentation in **1927**
- Occurs **nearly equally** in males and females (ratio of 1.2 to 1)
- The median age at diagnosis in patients in the (IFAR) was 7.6 years
- FA individuals with congenital anomalies are identified @ younger age
- Most patients attracts medical attention after development of hematopoietic complications.

Fanconi Anemia

- The **most frequent** genetic cause of bone marrow failure (BMF)
- Most patients are **only diagnosed** with FA at the onset of pancytopenia
- **>18 FA germline** gene mutations have been identified FANCA, FANCC, FANCG & **FANCD2**

“Most frequently involved in **DNA-replication dependent repair** of crosslinked DNA”

- When treated with MMC, FA cells accumulate chromosomal breaks and undergo G2 arrest, which is used as a diagnostic test.



Fanconi Anemia

- **Physical abnormalities** are present in 60%-75% of affected individuals “1 or more”:
 - Short stature,, malformations of the thumbs, forearms, skeletal system
 - Abnormal skin pigmentation
 - Malformations of eyes, ears
 - Malformations urinary tract. heart, (GI) system, (CN) system
 - Hypogonadism & Developmental delay
- In 25%-33% of FA patients, no physical anomalies are present at birth or in early childhood

“Diagnosed because of familial testing or development of BMF and/or other FA complications”

- Progressive bone marrow failure (BMF) with pancytopenia presents in the **first decade**
 - Often initially with thrombocytopenia or leukopenia.
 - **By 40 years of age**, the estimated cumulative incidence of BMF is 90%
- **The incidence of hematologic malignancies**, primarily MDS/AML; rarely ALL, or NHL, is **10%-30%**
- **The incidence of nonhematologic malignancies** (e.g. SCC of H&N , skin, GI tract & genital tract) is **25%-30%**

Frequency of congenital abnormalities in FA

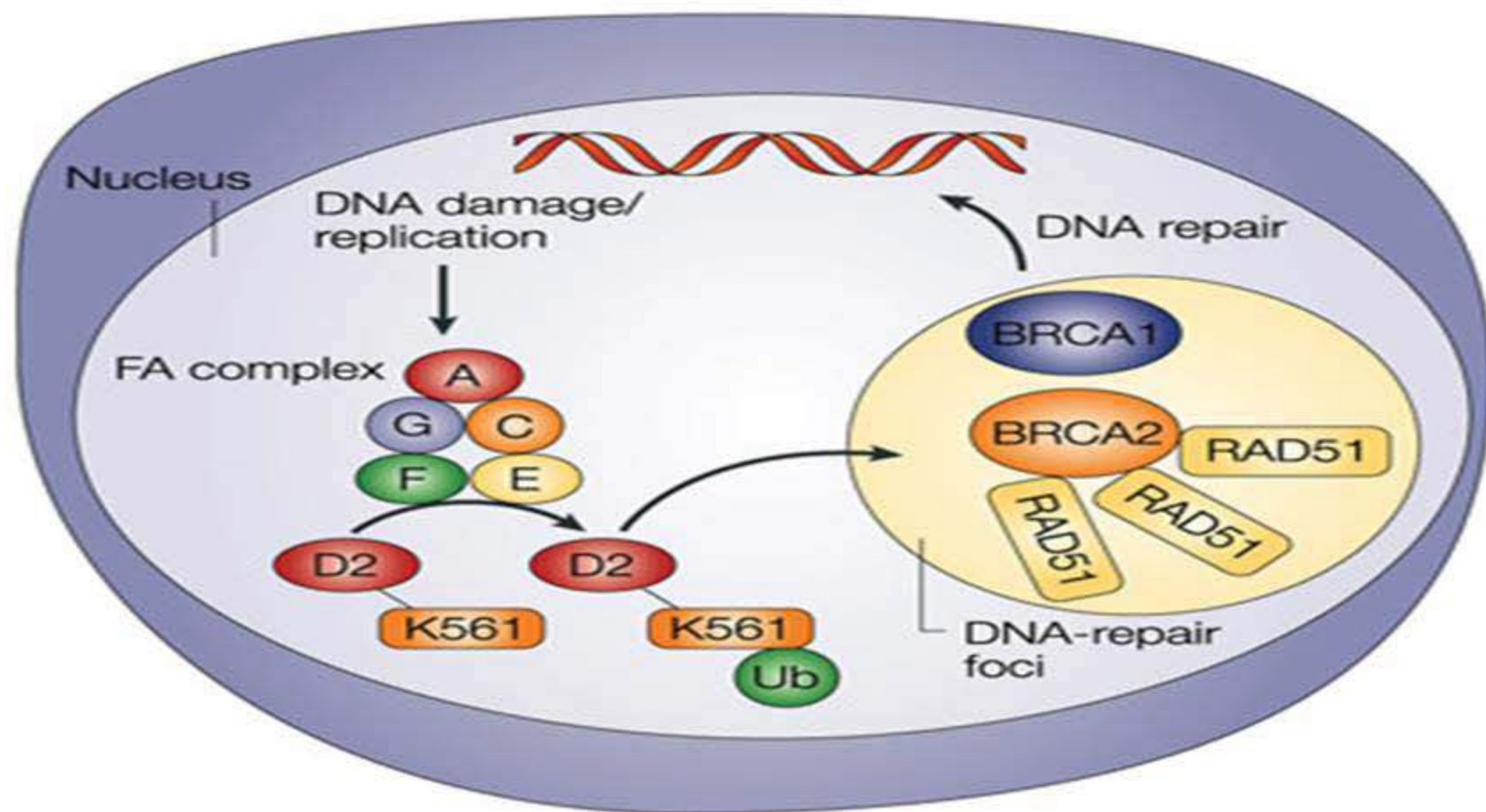
Anomaly	%
Skeletal	71
Skin pigmentation	64
Short stature	63
Eyes	38
Renal and urinary tract	34
Mental retardation	16
Gastrointestinal	14
Cardiac	13
Hearing	11
CNS	8
No obvious abnormalities	29

The FA/BRCA repair pathway

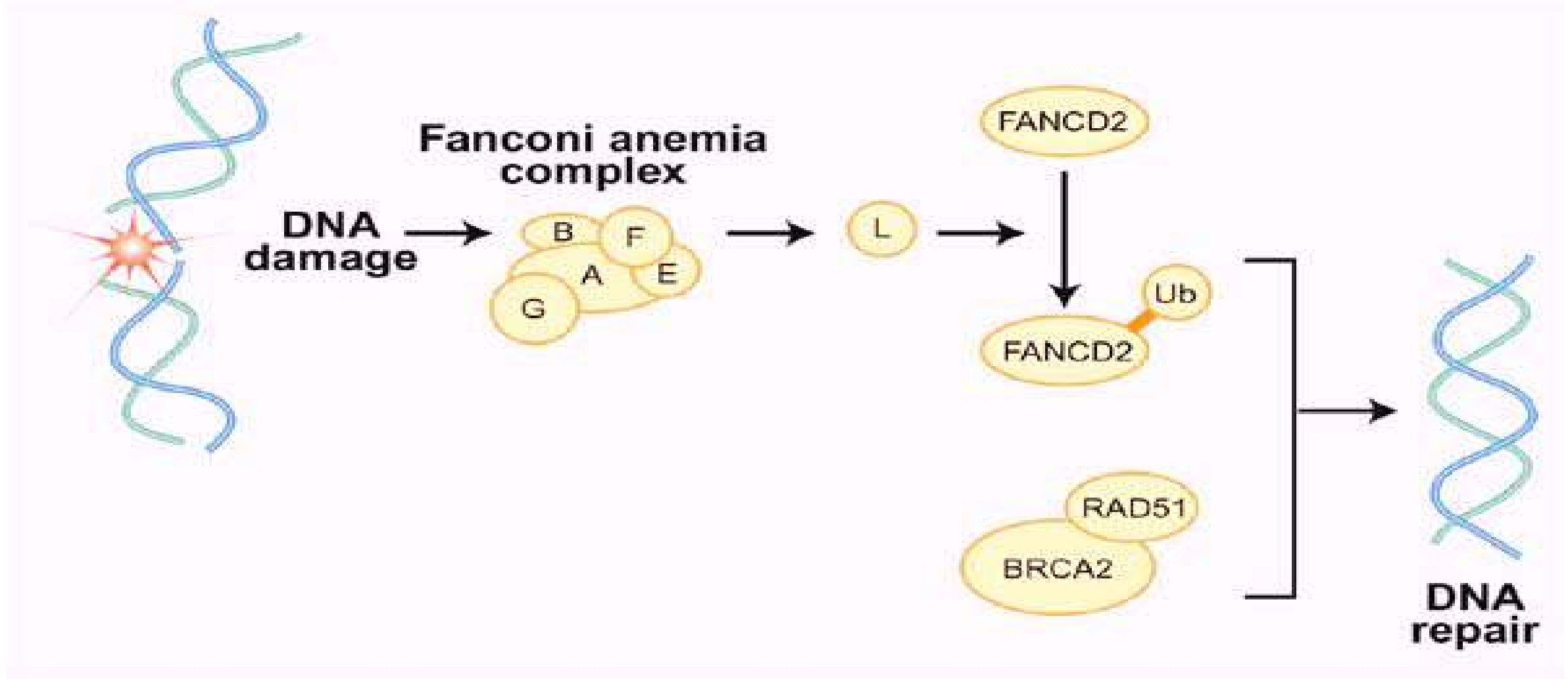
- At the cellular level, hypersensitivity to DNA interstrand cross linking agents is the defining feature of FA cells
 - Diepoxybutane, DEB
 - Mitomycin C, MMC
 - Cisplatin, CP
- Germline mutations interfere with DNA-replication dependent repair of crosslinked DNA

@ stalled replication forks

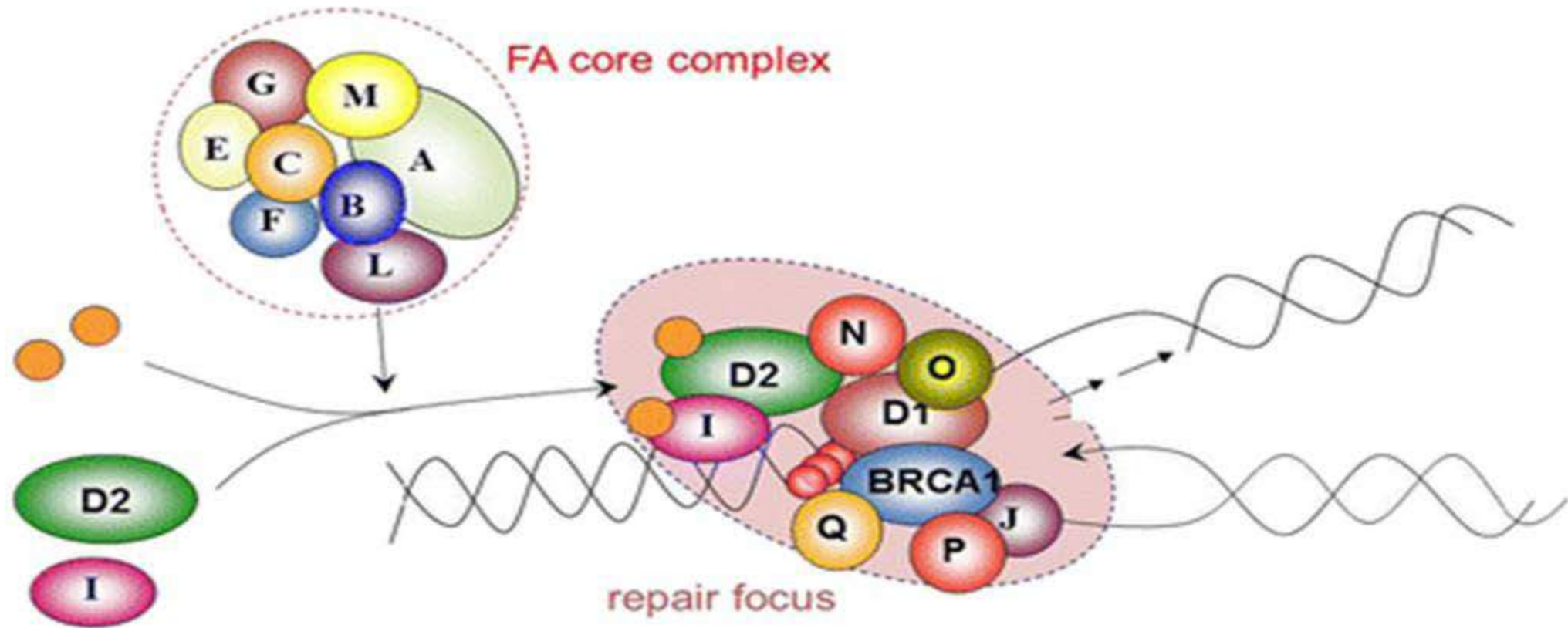
The FA/BRCA repair pathway



The FA/BRCA repair pathway



The FA/BRCA repair pathway



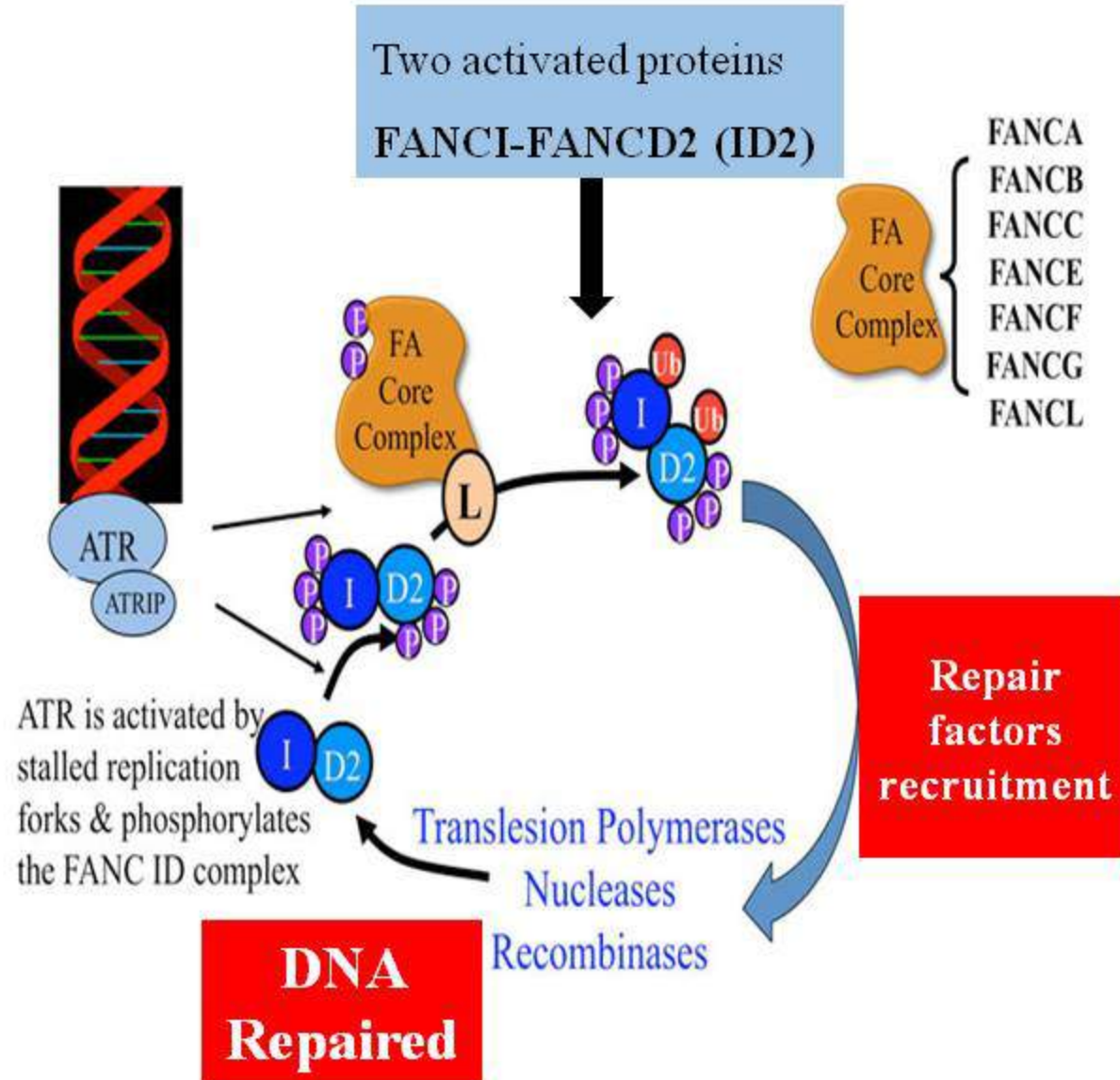
The two activated proteins **FANCI-FANCD2 (ID2)**, as a dimer, co-localize with other DNA repair proteins “**BRCA1, BRCA2, or RAD51**” in chromatin to form **repair focus**

FA pathway “ID Complex”

“ATR”

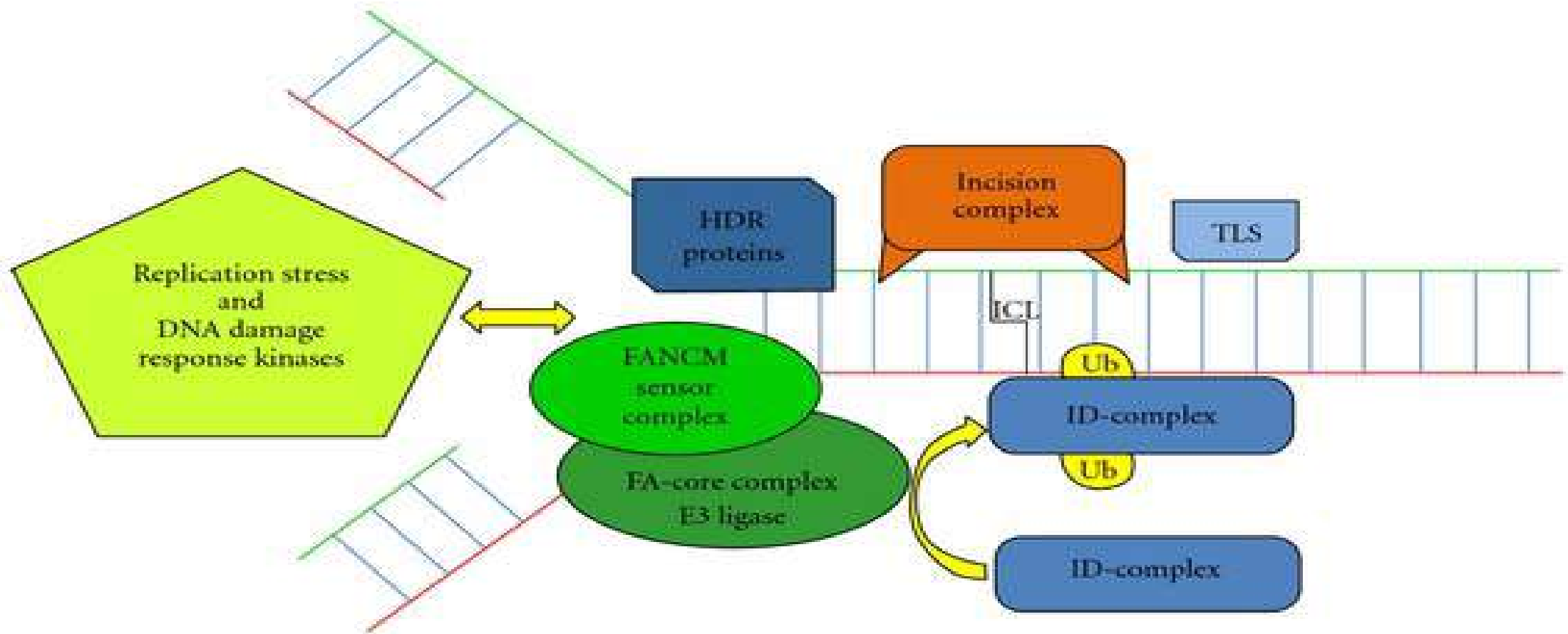
Serine/Threonine specific Protein Kinase

- **Sensing** DNA damage and **activating** DNA damage check points (Chk1)
- **Inducing** cascade downstream signal transduction phosphorylation leading to **Cell cycle arrest**
- **Activated in response** to **persistent single stranded** DNA which occurs at stalled replication forks
- **Starts DNA repair pathways** such as
 - Nucleotide excision repair
 - Homologous recombination repair

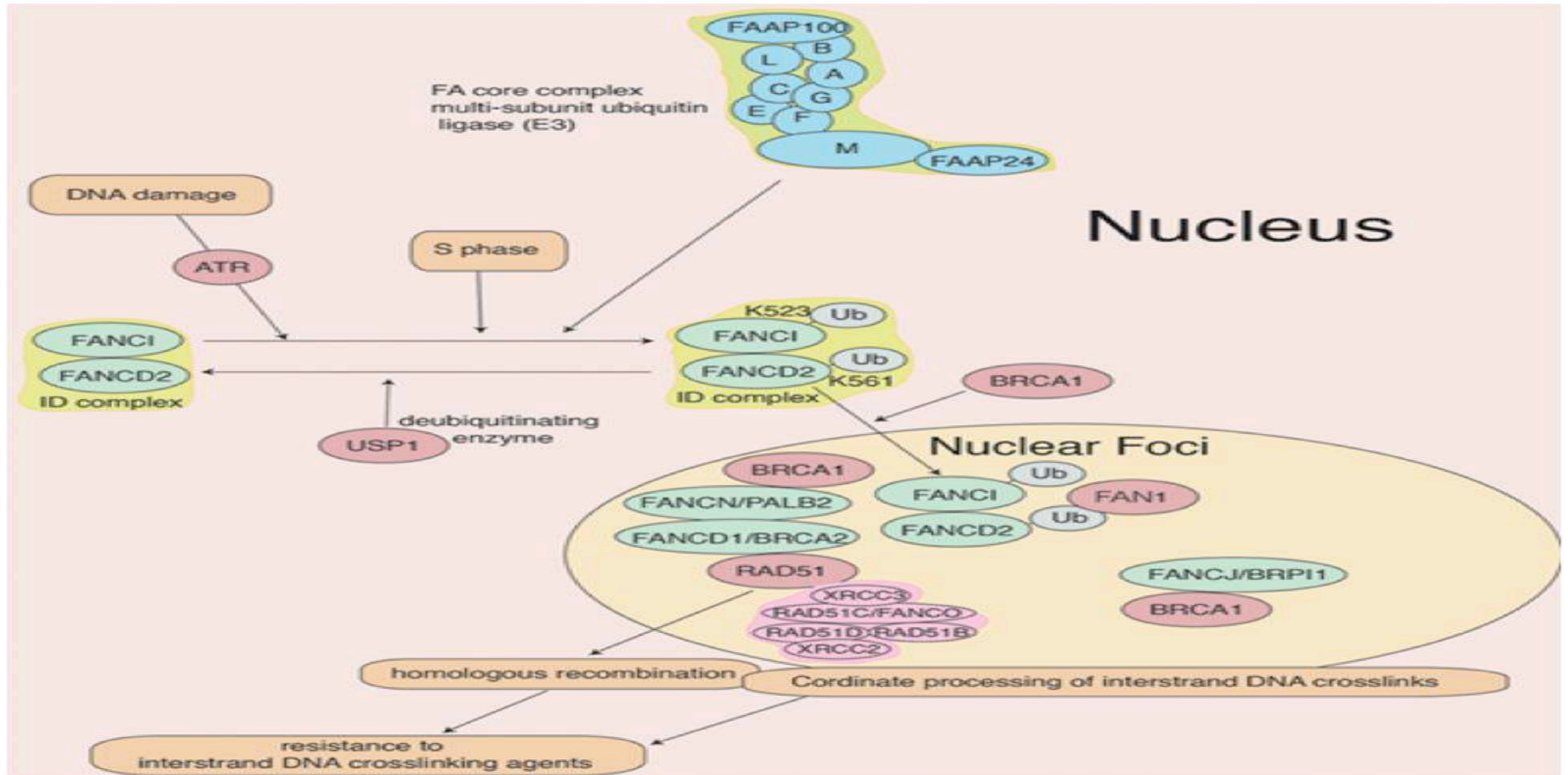


FA pathway “ID Complex”

Stalled replication forks



FA pathway “ID Complex”



The natural history of Fanconi Anemia

- **Progressive marrow failure** during early childhood “confirmed by chromosome breakage test”
- **The hematopoietic situation** throughout life may **change spontaneously** by:
 - Genetic reversion with “somatic mosaicism”
 - Clonal evolution toward MDS or AML
 - Biologically FA-MDS and FA-AML are characterized
 - Underrepresentation of the common cytogenetic and molecular subgroups
 - Overrepresentation of unbalanced chromosomal translocations “copy-number abnormalities”
- **Solid cancers** in adult FA patients is also high

Clonal evolution, MDS, and AML in FA patients

- Clinically, MDS and AML in FA are **often, but not always**, preceded by a BMF phase
- **AML** incidence of ranges from 10% to 37% by age 50 years
 - The most common time to develop leukemia being in the teenage years or young adulthood.
 - Although AML can be diagnosed de novo, more often it develops from an MDS phase with an increasing proportion of blast cells over months or years.
- **MDS** incidence in FA is reported to be 11% to 34%
 - Usually presents as RCMD with or without excess of blasts (WHO 2008).
 - Certain level of dyserythropoiesis is almost constant in FA patients **“mild dyserythropoiesis should not be considered an MDS”**
- **Isolated cases of ALL** : exceptionally reported

Clonal evolution, MDS, and AML in FA patients

- Throughout MDS and AML evolution,

A typical pattern of **acquired, nonrandom karyotypic** abnormalities
is associated with **BM clonal evolution**

- Classical de novo translocations such as t(8;21), t(15;17) & MLL translocations

Are **virtually absent**

- Unbalanced translocations and partial chromosome arm duplications or deletions are most frequent

Resulting in gains or losses of chromosomal regions

Clonal evolution, MDS, and AML in FA patients

- **Most frequent** abnormalities are :

1. The gain of chromosome 1q
2. The gain of chromosome 3q26q29
3. Deletion 7q
4. RUNX1 gene abnormalities at 21q22 (RUNX1-abn)

“Mutations involving genes other than RUNX1 are infrequent”

- Less frequently by 5q, 13q, and 20q deletions

Natural gene therapy

Somatic mosaicism

“special situation of FA”

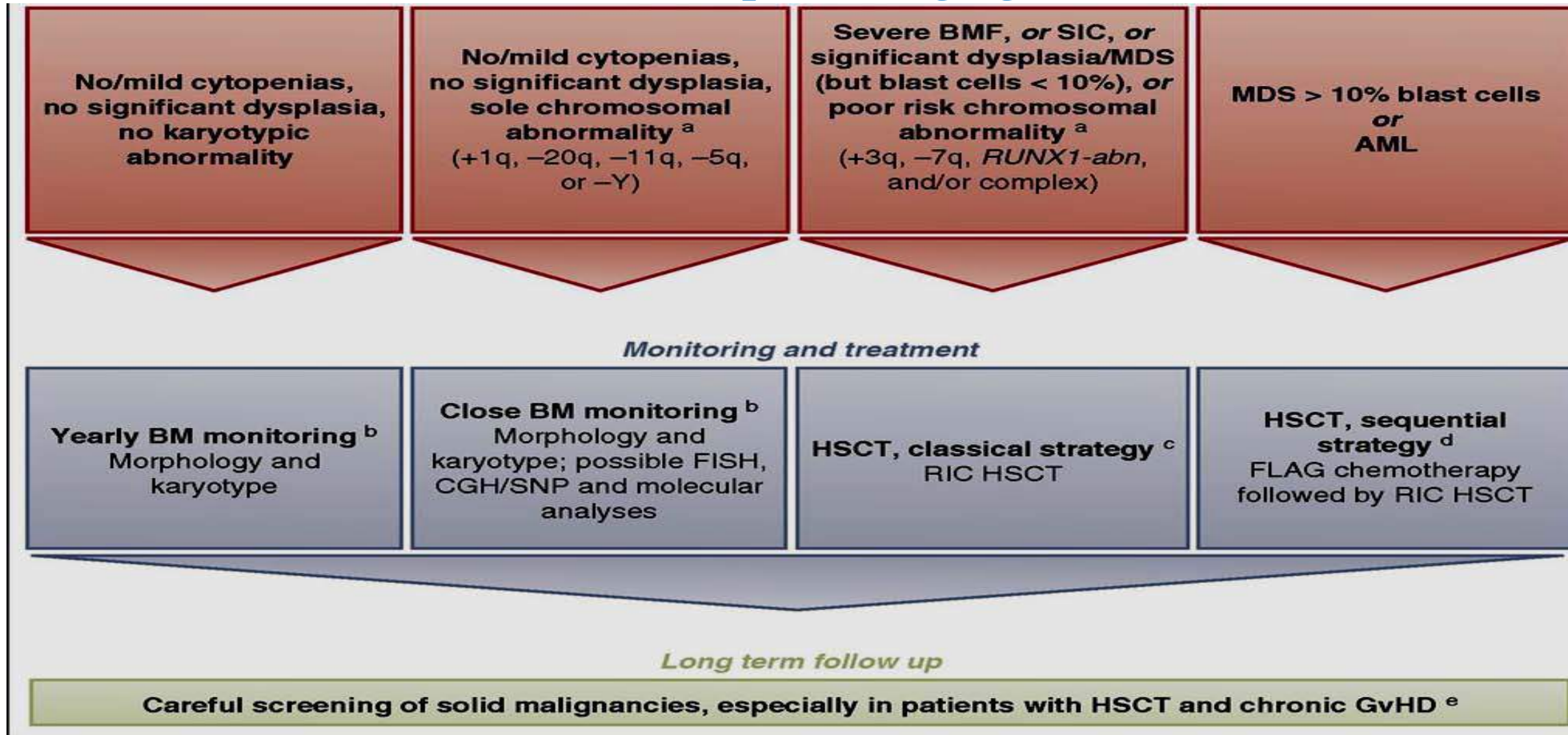
- ~17-25% undergo **somatic reversion** of **one of their two** germline mutations **FANC alleles** in at least **one** HSC
- Corrected progeny then repopulates the hematopoietic system resulting in normal blood and immune cells

Natural gene therapy

- Leads to genetic mosaicism with corrected & uncorrected cells co-existing in the same individual.
 - DNA crosslinker tests for FA in the PB (T cells under PHA stimulation), usually are normal & FA diagnosis is obtained via skin fibroblast testing
 - Many FA laboratories favor, analyses on primary skin fibroblasts
 - PB counts may be normal or only mildly depressed and do not experience BMF
- Clonal evolution from **nonrevertant bystander** cells into MDS/AML remains possible
- Just like HSCT, **does not offer** protection from solid cancers “2nd or 3rd decade of life”

How we manage FA?

BM workup and staging



“Diagnosis of an underlying (unknown) FA in patients with MDS or AML”

- Suspected in young patients with MDS or AML, especially when suggestive features are present:
 - Family history
 - Physical abnormalities, including short size
 - Spontaneous chromatid breaks
 - Unbalanced 1q, 3q, or 7q translocations on BM karyotype
 - Excessive toxicity of usual chemotherapy
- **Blood tests** especially after chemotherapy, may be technically difficult to confirm or exclude FA at the MDS/AML stage.
- **Nonhematopoietic cells** sensitivity to cross-linking agents (primary skin fibroblasts) is very helpful, but several weeks are required to grow the cells
- **Patient mouth wash or saliva cells** are highly contaminated by hematopoietic cells and are not a pure source of germ-line DNA.

Underlying (unknown) FA in patients with MDS or AML''

Remarks on BM

- The frequent occurrence of **BM dysplasia** **confounds** the diagnosis of MDS in FA patients.
- The universal finding of **dyserythropoiesis** as the sole abnormality is **insufficient** for the diagnosis of MDS in FA patients.
- **Hypocellularity** per se is **not a suitable criterion** for MDS in FA patients, especially cytopenias are usually present at diagnosis.
- **Increased blast count** is the **most reliable** morphologic evidence of MDS in FA

Underlying (unknown) FA in patients with MDS or AML''

Remarks on Cytogenetic abnormalities

- ~**35%** of BM from FA patients harbor cytogenetic abnormalities
- The clinical significance of **some** cytogenetic changes is **not clear**
 - Some clones may be transient & some persist for years without adverse clinical consequences
- **Certain** FA associated cytogenetic abnormalities are **nonrandom**
 - ~ 75% of these are unbalanced gains or losses in **1q+, 3q+, 7/7q-, and 11q-**

Patients with clonal cytogenetic abnormalities
are at **>10- fold higher risk** for developing MDS/AML (**35% vs. 3%**)

Treatment options

1. HSCT
2. Pretransplant cytoreduction
3. Androgens
4. G-CSF
5. Transfusions
6. Preventive measures

HSCT indications in FA patients with clonal evolution

In any FA case a donor search should not be delayed

“Keep in records”

- **FA W/O clonal evolution**: the optimal time for HSCT is the need for transfusion support (severe BMF or severe isolated cytopenia)

The **concept of preemptive transplant**, to preclude the development of leukemia or MDS has **not been fully addressed** in specific clonal evolution cases

- **FA patients with clonal evolution**, decision-making criteria for HSCT include overt AML and MDS with excess of blast cells, significant dysplasia, and/or poor prognosis cytogenetic abnormalities
- **FA with MDS/AML**: Allogeneic HSCT remains the only curative treatment (5 Y OS 30-40%)
- **FA with genetic reversion** (somatic mosaicism) but **W/o** severe aplasia or additional poor prognosis clone do not need HSCT.

Stem cell source and conditioning regimen

- **HLA-MFD HSCTs:** **CY based regimen** alone or **FLU/CY** “Excellent response”
- **HLA MUD HSCTs:** **FLU based RIC regimens** with or without T-cell depletion.
 - TBI (300 cGy) + CY + FLU and ATG “5-year survival probability of 94%”
- **AD** (ie, MMD, CB, or haplo-HSCT): still an option
- **The stem cell source**
 - BM cells is the recommended source > PBSCs “even in case of clonal evolution”
 - Less cGvHD & 2ry malignancies
- **GVHD prophylaxis:** Most commonly used combination is CSA + MMF

Long-term FU post-HSCT

New challenges!!

- Increased **risk of malignancy** post-HSCT (28% CI of solid malignancy by age 50 y)

German Fanconi Anemia Registry

- There is a **4.4-fold higher rate of SCC** in HSCT group compared no HSCT
- **Chronic GVHD** is also a key factor in increasing solid malignancies
- Every 6 months gynecology & ENT visits post HSCT

Pretransplant cytoreduction

**Secure a donor before offering
chemotherapy !!**

- **FA patients who develop MDS and/or leukemia**
 - The role of pre-HSCT chemotherapy **remains unclear**
 - **Not easy to manage** because sensitivity to DNA-damaging agents “Alkylators”
 - Cth is associated with **significant toxicity** “prolonged of aplasia & infections”

Complications can contraindicate future HSCT

Pretransplant cytoreduction

- One possibility is the use of **sequential chemotherapy strategy**
 - FLAG chemotherapy, followed 3 weeks later by RIC “FLU/CY/TBI”
- Some subsets of FA patients might benefit from cytoreduction before HSCT “several reports”
 - MDS with excess blasts/AML
 - BRCA2/FANCD1 patients

Androgen

- Increase/stabilize the **hemoglobin**
- Can also improve/stabilize the **platelet count**
- Used in **moderate** BMF

Start when hemoglobin < 8 g/dl or the platelet count falls < 30,000/mm³

- **Oxymetholone** is the standard recommended androgen
 - Response within 3 months
 - If no response is seen after 3-4 months → discontinued
 - Minimize the side effects by tapering the dose whenever possible.
 - Acne treatment with topical benzoyl peroxide and topical antibiotics (clindamycin or erythromycin)
- **Danazol** “synthetic androgen”
 - Few reports in the literature support its effectiveness
 - Fewer virilizing effects.

Side Effects of Androgens

- **Virilization** (acne, facial/ pubic hair growth, deepening of voice, enlargement of penis or clitoris)
- Growth spurt followed by **premature closure of epiphyses** and short adult stature
- **Behavioral changes** (puberty, aggressiveness)
- **Cholestatic jaundice** or transaminitis
- **Peliosis hepatis**
- **HTN**
- Long term androgen treatment “**predominantly with oxymetholone**”
 - Liver adenomas → Malignant transformations to adenocarcinoma
 - Testis atrophy in males, due to suppression of the hypothalamic-pituitary-gonadal axis.

Cytokines “G-CSF”

- May be considered if the neutropenia is associated with recurrent or serious infections, particularly
 - If the neutrophil counts persistently $< 500/\text{mm}^3$
- Discontinued if the neutrophil count fails to improve **after eight weeks** of therapy

- BMA/BMB with cytogenetics is recommended **prior to the initiation** of cytokine treatment

- Monitor the BM morphology and cytogenetics **every six months** while patients on cytokines

Transfusion of blood products

- **Blood transfusions** “maintain minimal trough hemoglobin levels, usually 7-8 g/dl”
 - Manage symptoms of anemia “allow for normal activity”
 - Normal growth & development
 - Before surgery
- **Platelet transfusions** : significant bleeding (thrombocytopenia) or prior to surgery.
 - HSCT should be discussed/considered when the platelet counts fall $<50,000/\text{mm}^3$.
 - If transplant is not pursued, then give androgens if platelet count $< 30,000/\text{mm}^3$.
 - Avoid drugs that inhibit platelet function “aspirin or NSAID (e.g., ibuprofen)

Preventive measures

HPV vaccination

- Recommended because it cannot be excluded that HPV contributes to FA-associated neoplasms
- Both genders should be vaccinated.

ENT examination

- 2/3 of Head and Neck SCCs in FA patients are located in the oral cavity
- Surveillance importance is underscored
 - High incidence of H&N SCCs, combined with the limited therapeutic options “Rth & Cth”
- Every 6 monthly/starting age
 - 10-12y after HSCT
 - 14-15y without HSCT

Preventive measures

Gynecology exams

- **Female FA patients** face a variety of gynecological problems such as
 - Structural abnormalities ---- Delayed puberty
 - Decreased fertility ----- early menopause
 - High risk of SCC of the cervix, vagina, vulva, and anus
 - Breast and ovarian cancer later in life.
- Yearly gynecological evaluation by 12 y and annual cervical examinations by age 18 y
- Birth control needs to be carefully evaluated and discussed with the families.
- If not transplanted, hormonal contraception “ not ideal”: effects on the hematopoietic system.
- Pregnancy is classified as HR and menopausal symptoms may present at a young age

Preventive measures

Annual endocrine evaluations

- Endocrine abnormalities occur frequently in FA patients
- The affected systems often include
 - GH regulation,
 - Thyroid hormones
 - Glucose metabolism
 - Gonadal hormone productions
- Appropriate testing may include:
 - 8:00 am TSH and FT4
 - Oral glucose tolerance test, HbA1c
 - 25OH vitamin D
- **If the growth rate is too slow:** AM FT4, TSH, IGF-I, IGFBP3, bone age,
- **If delayed puberty:** LH, FSH, Estradiol or Testosterone, DXA (bone density scan), bone age

Thank You