

**IN
THE
NAME
OF
GOD**

Thrombocytopenia in Childhood

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Thrombocytopenia in children

- **Thrombocytopenia** is one of the most common hematological complications found in **neonates and children** in the daily practice.
- As the **etiologies** of thrombocytopenia are various from **congenital causes to acquired causes**
- Thrombocytopenia could be the results of impaired production, increased destruction/consumption and abnormal sequestration, those make the diagnosis of thrombocytopenia in neonates and children **more challenging**

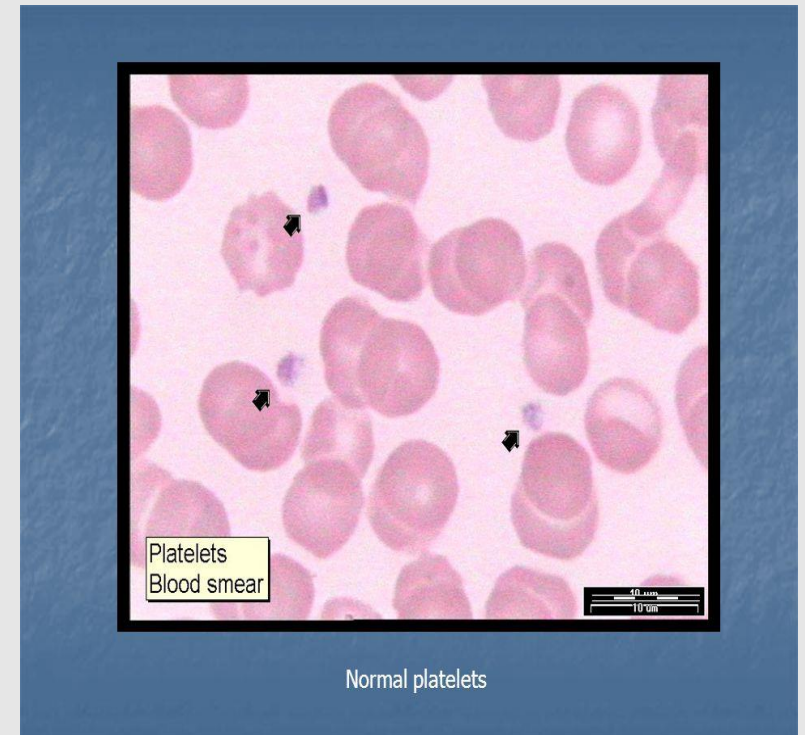
A12 mo boy

present to Hematology clinic :history of Thrombocytopenia and respiratory infection

PE: Eczema , purpura.

WBC ; 10000 PMN : 45% L : 40 % M: 2% HB: 11 Platelet; 15000/ uI

What is your Diagnosis??



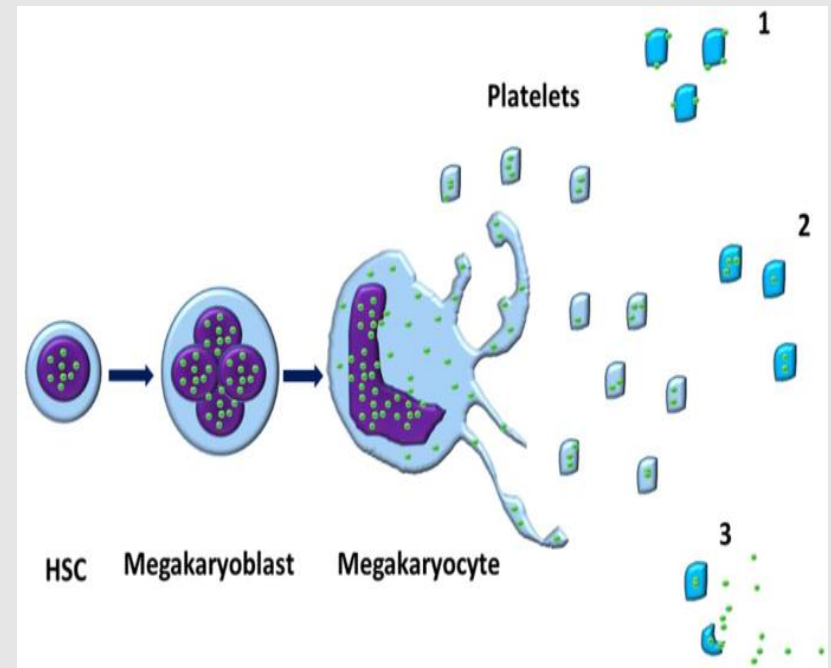
Normal platelets

Thrombocytopenia in Children

- Thrombocytopenia :a platelet count of $<150,000/\text{mL}$.
- NL range platelet count : **$150-450 \times 10^9/\text{L}$**
- Thrombocytopenia :clinically suspected when there is a **history of easy bruising or bleeding (..nasal bleeding)**
- Thrombocytopenia presentation : vary,may be present as an **incidental finding during routine evaluation or during investigations performed for other reason, or Fetal presentation**

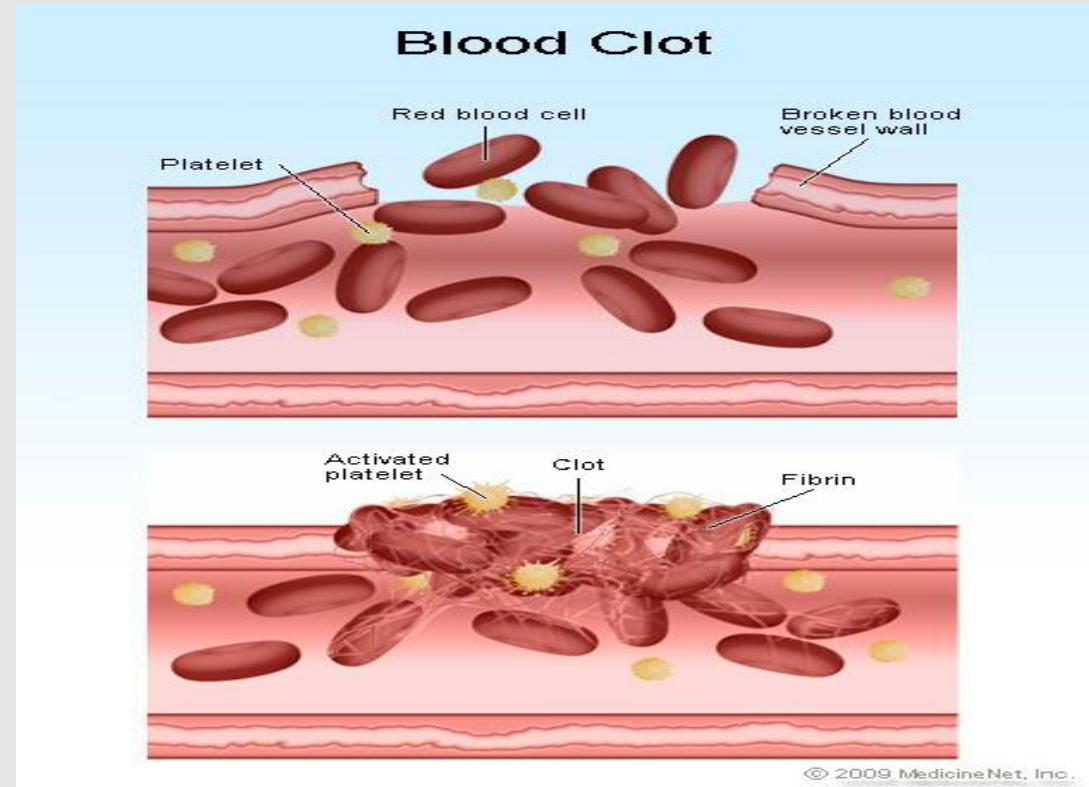
Source of platelet

- **Source :**
- Non nucleated cellular fragments by **Megacaryocytes in Bone Marrow**
- **Life span : 10-14 days**
- **Growth factor ;
Thrombopoietin(TPO)**



Hemostatic Function of platelet

Role of platelet : ○
Hemostatic role in
association with Von
willebrand factor ,
fibrinogen , (
adhesion and
aggregation) platelets



Approach to thrombocytopenia (Bleeding disorder)

- History and Physical Examination:
- Age
- Male or Female
- Type of Bleeding (Deep bleeding vs superficial & mucosal,...)
- Associated Sign and symptoms
- **Familial History**
-

SIGN & SYMPTOMS BASED OF THROMBOCYTOPENIA

Definition of thrombocytopenia:
platelet (PLT) count $< 150,000/\mu\text{L}$

SIGNS AND SYMPTOMS

Platelet ($\times 10^3/\mu\text{L}$)	Example of Bleeding Risk
> 100	Asymptomatic
50 - 100	Post-operative bleeding & bruising
20 - 50	Petechiae, purpura, ecchymoses
5 - 20	Epistaxis or gingival bleeding
< 10	GI bleeding, heavy menstrual bleeding or intracranial hemorrhage

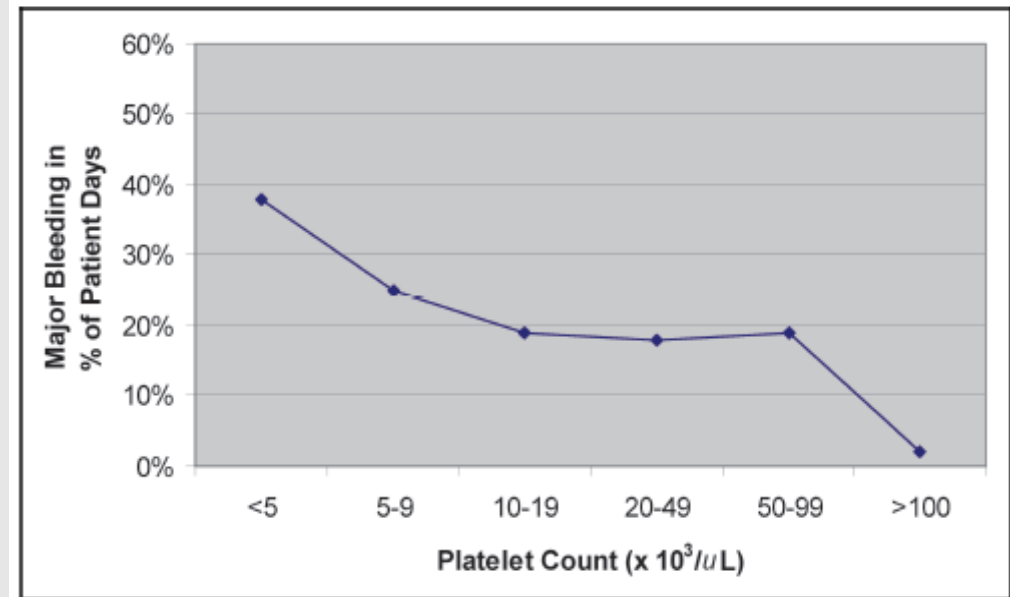







Figure 1. Relationship between major bleeding and platelet count. Adapted from Slichter SJ. Relationship between platelet count and bleeding risk in thrombocytopenic patients. *Transfus Med Rev.* 2004;18:153-167.

PRESENTATION of THROMBOCYTOPENIA IN CHILDREN .

Usman Ahmed (MD 2022, University of Alberta) & Dr. Mark Belletrutti (Pediatric Associate Professor, University of British Columbia) for Hematology and Clinical

PRESENTATION	
HISTORY	PHYSICAL EXAM
<p>Bleeding Hx</p> <ul style="list-style-type: none">Provoked (trauma, surgery) or spontaneousDeep or superficial bleeds <p>Red Flag Symptoms</p> <p>! Fever, weight loss, night sweats, bone pain, fatigue</p> <ul style="list-style-type: none">Prodromal illnessRecent live vaccination (MMR)Recent travelDietary HistoryFamily Hx of bleeding disordersReview Medications listIf newborn ask about maternal PLT count, medical history and medications	<ul style="list-style-type: none">ABCs and vital signs (stable or unstable) Purpura, petechiae, ecchymoses, mucocutaneous bleeding Altered consciousness, abnormal pupils, slurred speech Lymphadenopathy (malignancy)Hepatosplenomegaly Swollen joints or rash <p>INVESTIGATIONS</p> <p>CBC (isolated PLT vs. pancytopenia)</p> <ul style="list-style-type: none">Check previous PLT counts <p>Peripheral blood smear</p> <p>Bone marrow examination ONLY IF:</p> <ul style="list-style-type: none">! Red Flag Symptoms ! Involvement of other blood cell lines (anemia or neutropenia)! Blasts on smear

DIFFERENTIAL DIANOSIS in THROMBOCYTOPENIA of Children

Usman Ahmed (MD 2022, University of Alberta) & Dr. Mark Belletrutti (Pediatric Hematology . Published August 2021
Associate Professor, University of British Columbia) for www.pedscases.com.and Clinical

DIFFERENTIAL DIAGNOSIS			
Thrombocytopenia			
PLT Destruction		Decreased PLT Production	Splenic Sequestration
Immune Mediated	Consumptive		
Immune Thrombocytopenia	Hemolytic Uremic Syndrome	Malignancy (leukemia, lymphoma)	Hypersplenism (infection, sickle cell, malignancy)
HIV, Hep C	Disseminated Intravascular Coagulopathy	Medications (chemotherapy)	Von Willebrand Disease
Neonatal alloimmune thrombocytopenia		Infectious (sepsis, viral)	
Lupus, Juvenile Idiopathic Arthritis		Nutritional deficiencies (B12, folate, iron)	
Neonatal autoimmune thrombocytopenia		Inherited & Congenital (Wiskott-Aldrich Syndrome)	

Question???

**Isolated thrombocytopenia
in childhood:**

Immune thrombocytopenia?

what ???????

if it is not

Causes of childhood thrombocytopenia that mimic immune thrombocytopenia

Thrombocytopenia secondary to immune disorders

- Systemic lupus erythematosus . SLE
- Primary immune deficiencies : PID
- Autoimmune lymphoproliferative disorder. ALPS

Constitutional bone marrow failure syndromes/congenital disorders

- Congenital amegakaryocytic thrombocytopenia
- Fanconi anaemia
- Wiskott-Aldrich syndrome
- X-linked thrombocytopenia
- Myosin heavy chain 9-related disorders(MYH- 9 anomaly)
- Congenital infection syndromes

Causes of childhood thrombocytopenia that mimic immune thrombocytopenia

❑ Acquired Bone Marrow failure

- Aplastic anaemia , Idiopathic or
- Leukaemia and other malignancies with marrow infiltration

Consumptive thrombocytopenia

- Hypersplenism
- Thrombotic microangiopathies

Specific infections

- Malaria , Human immunodeficiency virus infect .

Immune thrombocytopenia of childhood

- Childhood immune thrombocytopenia (ITP) remains a diagnosis of exclusion other disorders.
- Incidence of 4.0– 5.3 per 100,000, presentation : Plate < 20000
- Presentation : Acute abrupt onset ,1-4 weeks after viral infection ??(Mumps ,EBV , HIV , ;.....)
- History of Live Vaccination (MMR) ???
- Age ; 1-4 Y usually
- Pathogenesis: Binding of AB to platelet surface, recognize by FC receptors of on splenic Macrophages & Destruction .
- presentation : No symptoms , bruising- petechiae , Epistaxis ,Menorrhagia , Melena ,rare ICH(intra cranial hemorrhage)
- Severe life threatening bleeding is rare (0.2–0.9%)

Immune thrombocytopenia /ITP in Children

- Differential Diagnosis, should be careful about : Leukemia , Collagen Vascular disease (CVD) , Bone marrow failure syndromes Infections
- **Lab Data in DD :**
- Low plate < 20000. HB & WBC , Diff : NI Size of platelet (MPV) NL or high
- **BMA : is it necessary to do in ITP ???**
- BMA : MEG in BM NL or or increase , **WBC & Erythroids :NL**
- Collagen vascular tests (SLE , ...) ,Coombs tests
- HIV , ,.....
- Helicobacter Pylori , more in adults
- Fanconi Anemia . Congenita Dyskeratosis , PNH ./ DEB test - Ch Fragility test , length of telomer, CD55, CD59 Flowcytometry
- **Gene Analysis : Congenital Amegacaryocytic Thrombocytopenia , Dys keratosis congeniat , ,.....**

Immune thrombocytopenia /ITP in Children

- To treat or not to treat?
- What treatment to use?

Management :

- Usually Benign, self-limiting course, with or without treatment.
 - Treatment ; No effect on outcome
 - safe level $> 20 \times 10^9 / L$ is target

Immune thrombocytopenia /ITP in Children

Management:

- **Observation only**
- **The use of intravenous immunoglobulin (IVIG), steroids, anti-D immunoglobulin, each alone or in combination**
 - ✓ single dose IVIG 0.8 -1 gr/ kg x 1-2 days, rapid rise in 95% in 48 hour , side effects : Headache , Aseptic Meningitis .
 - ✓ Short course corticosteroid prednisone 1-4 mg / kg / day . usually prednisone 2mg /kg / day x 14 days then taper and dc .
 - ✓ IV anti d, in Rh pos patients : 50-75 ug/ kg / day , side effects : Hemolytic anemia
- **No plate transfusion ?? Just in life threatening bleeding .**

Immune thrombocytopenia /ITP in Children

- Patients of ITP about 20 % > 1 year : chronic ITP
- **Treatment :**
 - Immunosuppressive therapy
 - Rituximab (Anti CD 20 monoclonal AB)
 - Splenectomy in children ITP ??????? : Late & less use
 - Recently : Thrombopoietin (TPO) agonists (Romiplostim and Eltrombopag) with good response in adult and pediatric patients with severe chronic ITP

Inherited Bone Marrow Failure FANCONI ANEMIA.

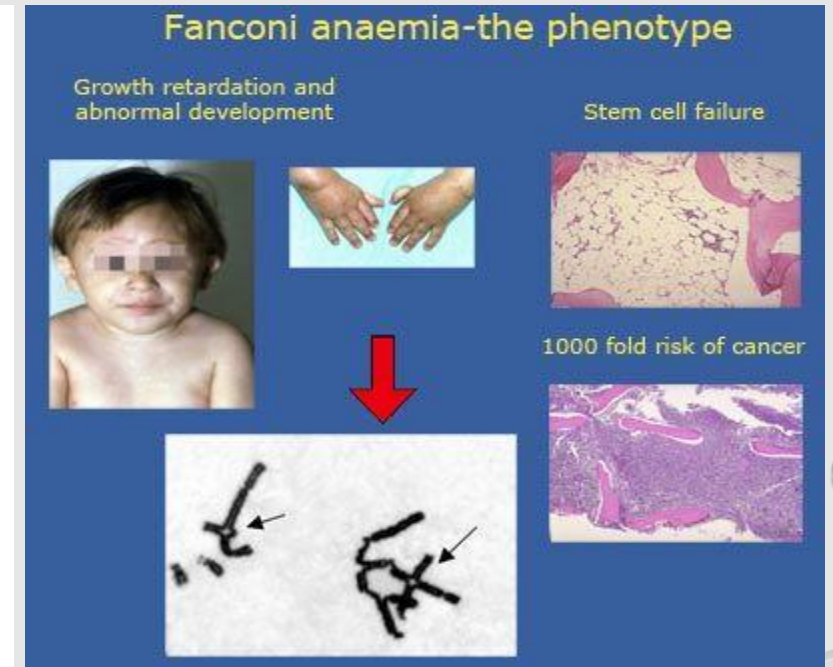
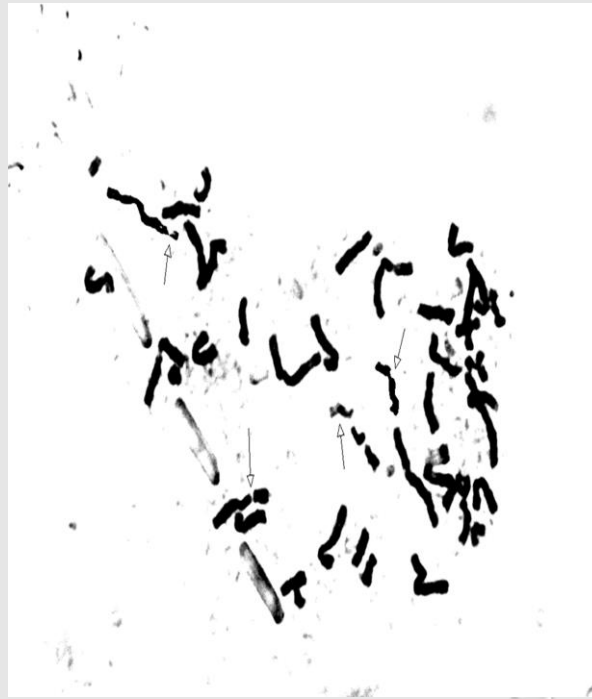
Autosomal Recessive , 1st decade of life. 21 FANC gene mutation

Triad : Bone marrow failure (BMF) + congenital anomalies + Defect in DNA repair & increased of ch fragility (DEB- diepoxybutane) & mitomycine c (MMC)

BMA & BMB : Hypocellular

predisposition to Malignancy: (MDS, AML , epithelia cancer)

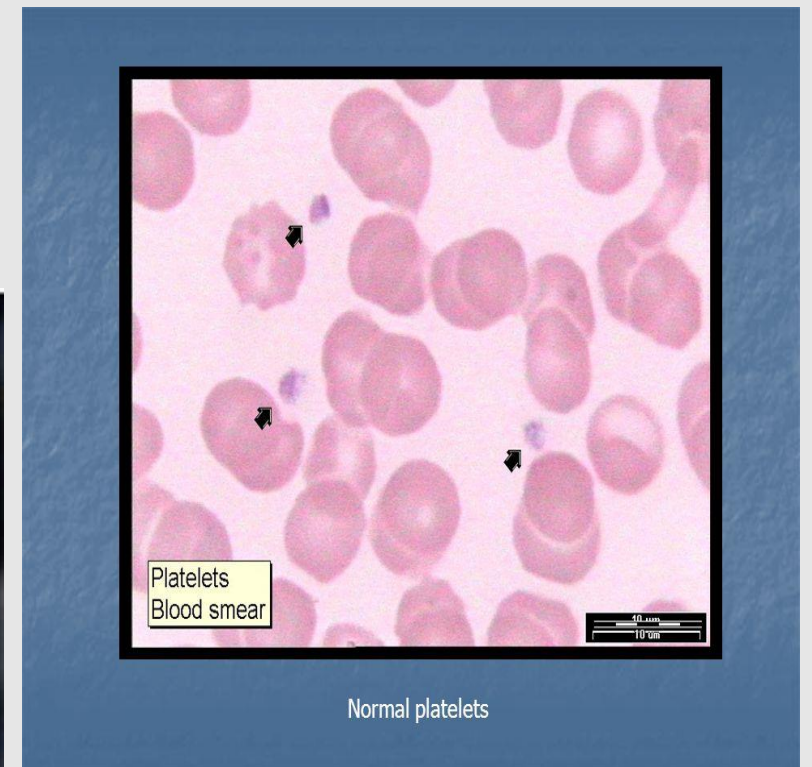
CURE : HSCT



Primary Immune Deficiency

Wiskott Aldrich syndrome .X linked . Micro-Thrombocytopenia , Eczema , Recurrent infections, immune cytopenia

Cure :ALLO -HSCT



Drugs & Thrombocytopenia

Immune and Nonimmune.

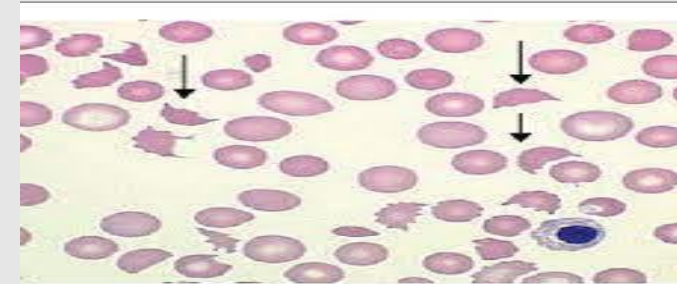
- **Mechanisms: Immune Process or Megacaryocyte injury.**
- **Valporic acid**
- **Phenytoin**
- **Carbamazepin**
- **Sulfanamides**
- **Vancomycin**
- **Heparin induced thrombocytopenia**
-



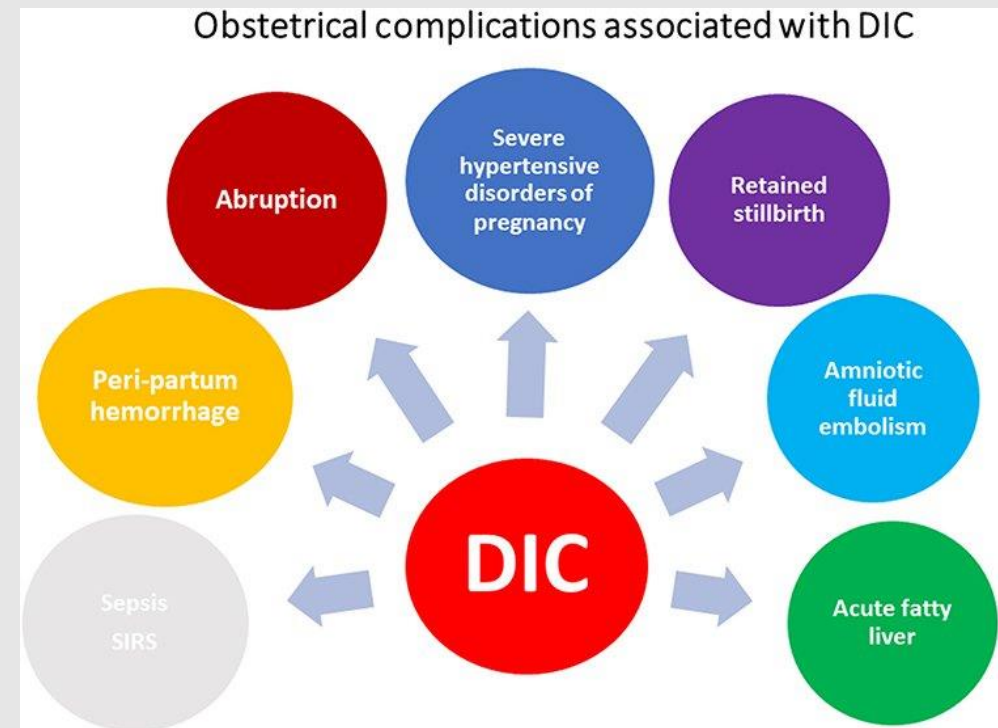
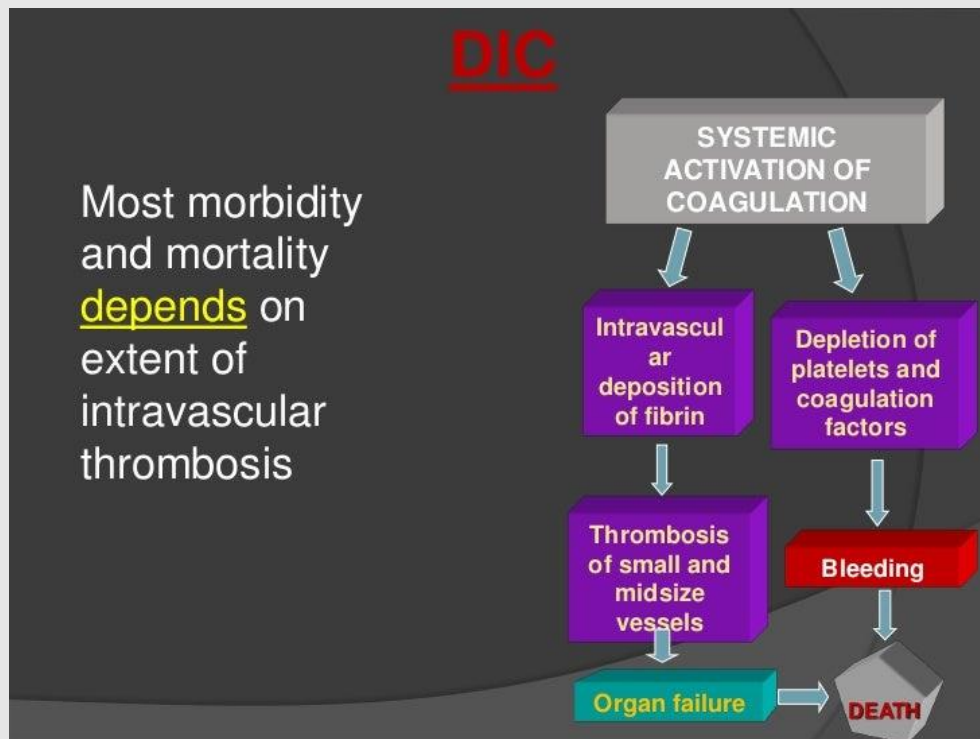
Hemolytic Uremic Syndrome

Acquired Acute renal failure in Young children

- **Triad ; Micro angiopathic Hemolytic Anemia, Thrombocytopenia , Renal Failure**
- **Etiology ? : Infection , Medication , Genetic**
- E coli toxin ; diarrhea associated O157 : H7, & shigella Dysnteri type 1 or shiga like toxins and Strep pneumoniae
- Diagnosis: Thrombocytopenia , Anemia , Schistocytes in PBS , kidney involvement , urine Hematuria & Pr- uria
- Treatment : Supportive therapy



DISSEMINATED INTRAVASCULAR COAGULATION_ DIC



Lab Data & Treatment OF DIC

Laboratory Findings in Acute DIC

- Platelet Count		↓
- Fibrinogen		↓
- PT (INR)	↑	
- PTT		↑
- D-dimer	↑	
- Peripheral smear	Schistocytes, helmet cells	

DIC - TREATMENT

- Treatment of the precipitating factor
- Bleeding treated with FFP, thrombocytes, cryoprecipitate
- Thrombosis treated with heparin, LMWH

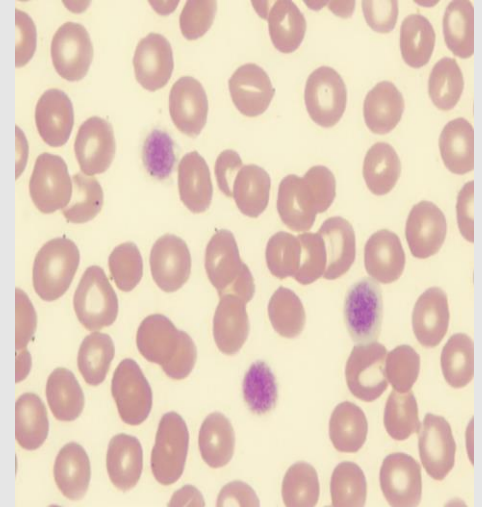
Newest treatments

- Activated Protein C
- TFPI
- Anti-thrombin

Inherited Platelet function defect

Bernard Soulier syndrome

- Autosomal Recessive Bleeding disorder
- GpIb complex , On the plate membrane
- **Trombocytopenia & Giant platelet (Interaction with plate cytoskeleton)**
- Prolong BT > 20 min & prolong PFA
- **Treatment :**
 - Antifibrinolytic agents , Desmopressin
 - plate transfusion, (be careful for Ab formation and Alloimmunization), Off label use of Recombinant VIIa factor
 - HSCT some times



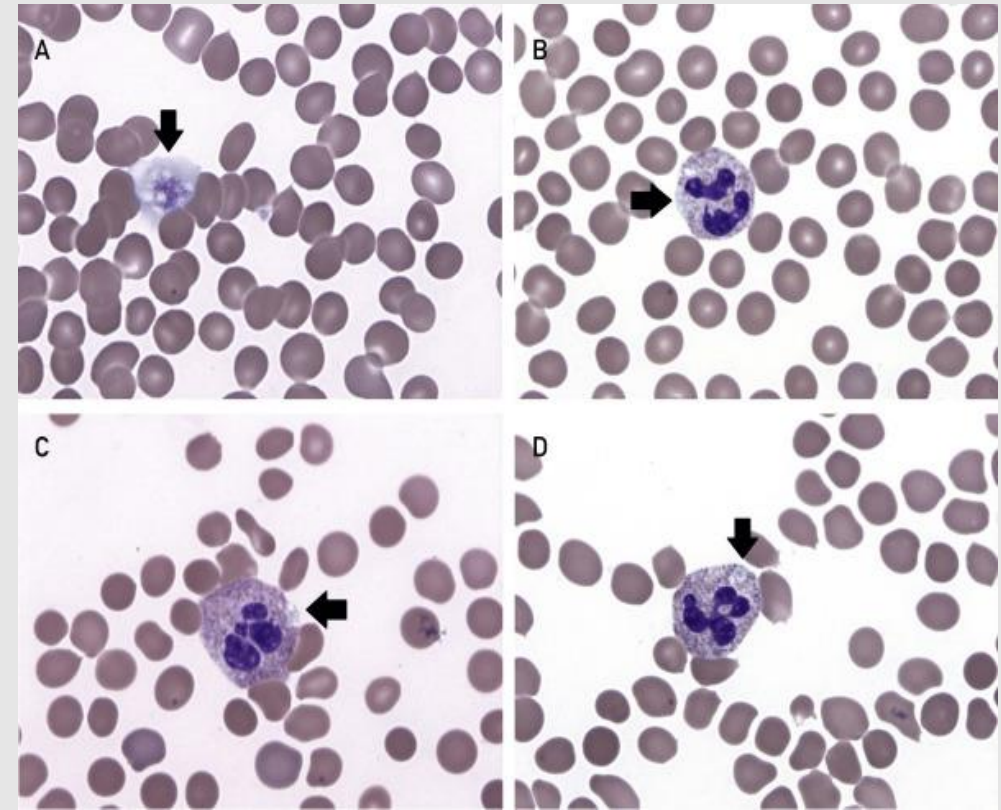
MYH9 related disorders

Congenital Thrombocytopenia Ch 22q1213

- **4 separate disorders: MayHegglin anomaly ,Epstein, Fechtner and Sebastian syndromes.**
- **Today's Re named MYH9-related disorder.**
- **Presentation : Bleeding problems, Hearing loss, kidney (renal) disease, cataracts.**
- platelets size are larger than normal. **High MPV**
- 33 mutations in the MYH9 gene, More than 200 affected families Autosomal dominant pattern
- **Gene: a protein called myosin-9. This protein is one part (subunit) of the myosin IIA protein**

MYH9-Related Thrombocytopenia. May-Hegglin anomaly

- **A 12-Y-old male** :Enlarged hematoma on his **Right calf secondary to minor trauma.**
- **CBC : platelets, 25 000/ μ L.**
- **Patient's mother** :chronic thrombocytopenia
- **PBS :Giant platelets & neutrophils with Döhle-like bodies**
- **Diagnosis:** MYH9-related thrombocytopenia.
- **Manage :** conservatively with rest, ice, compression, and elevation and then discharged home.



TAR Syndrome

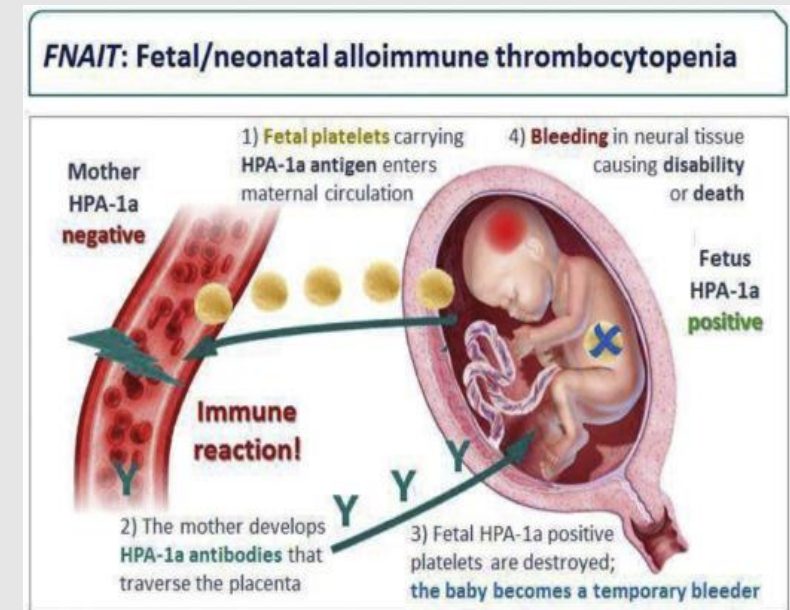
- **Thrombocytopenia absent radius (TAR) syndrome : AR**
- Bilateral absence of the radii with the **presence of both thumbs** and **thrombocytopenia** (<50 platelets/nL) **that is generally transient**.
Thrombocytopenia may be congenital or may develop within the first few weeks to months of life
- **Skeleton , GU anomalies**
- **Cow's milk allergy is common**



Thrombocytopenia in Neonates

Neonatal Alloimmune Thrombocytopenia NATP

- Low platelet / Neonates ; Systemic ,Maternal Ab transfer against platelet of fetus
- NATP : 1/4000- 1/5000 .
- presentation ; low thrombocytopenia , petechiae , purpura,
- 30 % ICH
- Normal plate of mother
- **The most common : plate alloantigen HPA 1a**
- DD ; Maternal ITP , viral & Bac infection
- Treatment I; IVIG for mother prenatally , Cesarean section& washed maternal plate & Informed parents for next pregnancy



Conclusion

- **Thrombocytopenia in Children has many Differential Diagnosis(DD)**
- **History & Physical Exam are first steps and main factors for correct Diagnosis & Treatment**

Thank You

