CHILD WITH BLEEDING DIATHESIS

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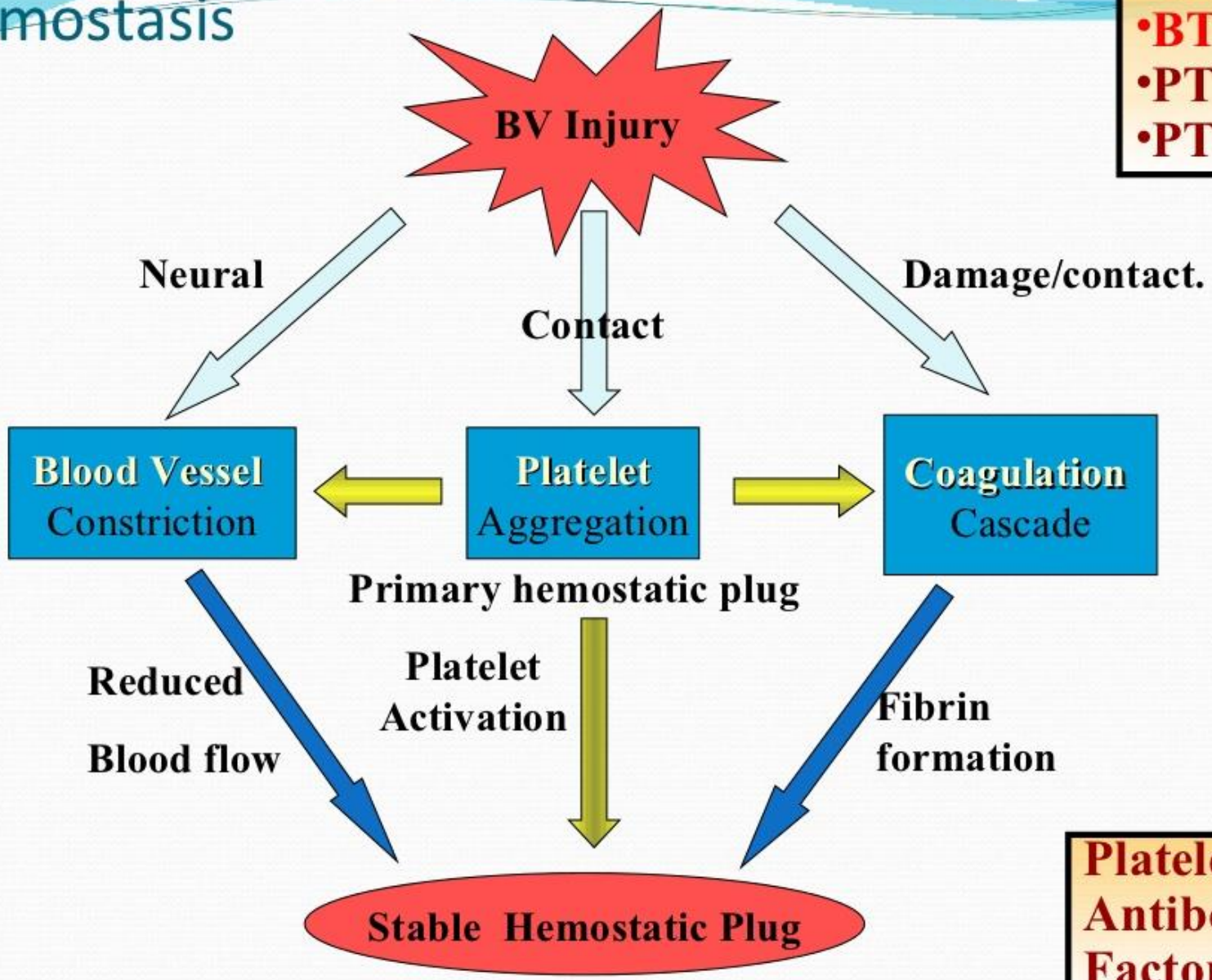
BLEEDING TENDENCY

- Bleedings that occur spontaneously or excessively after a trauma, not appropriate for the severity of trauma
- Clinically

✓ Duration is prolonged (oozing from the site of tissue injury may last for hours, days or weeks)

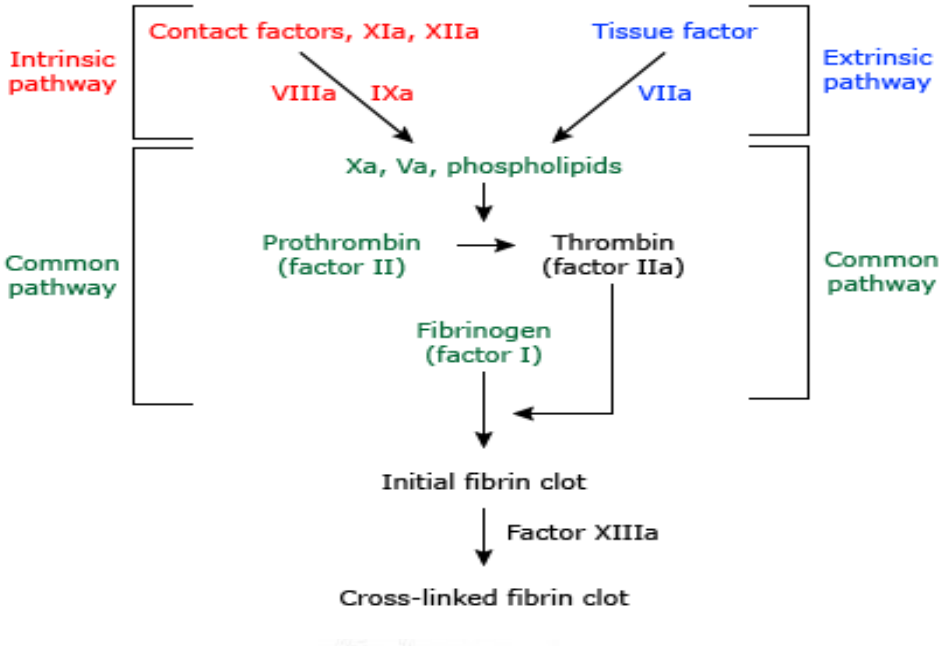
✓ Intensity is usually not very high (not as profound as in arterial cuts)

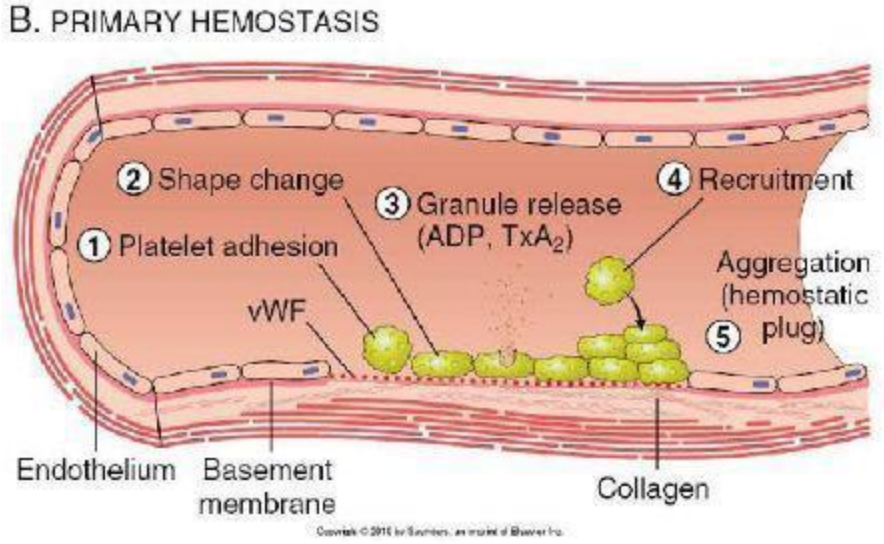
Hemostasis

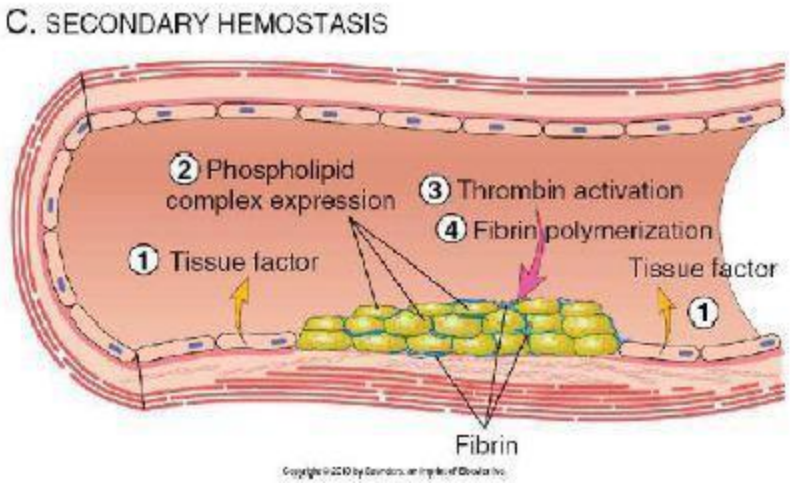


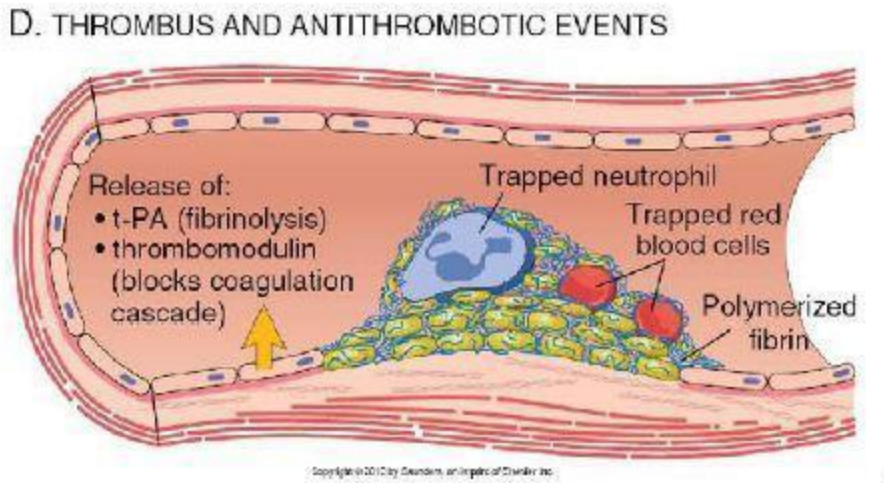
- CBC-Plt
- BT,(CT)
- PT
- PTT

Platelet study
Antibody tests
Factor Assay


Intrinsic pathway
Contact factors, XIa, XIIa
Tissue factor
Extrinsic pathway
VIIIa
IXa
VIIa
Xa, Va, phospholipids
Common pathway
Prothrombin (factor II)
Thrombin (factor IIa)
Common pathway
Fibrinogen (factor I)
Initial fibrin clot
Factor XIIIa
Cross-linked fibrin clot

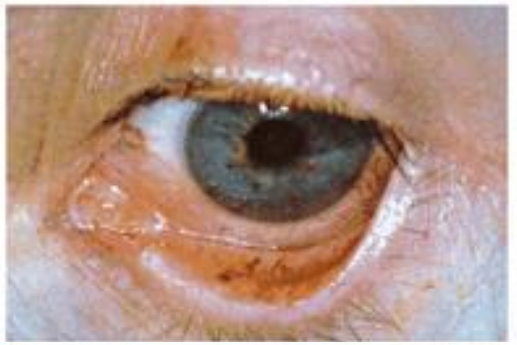

B. PRIMARY HEMOSTASIS
2 Shape change
3 Granule release (ADP, TxA2)
4 Recruitment
1 Platelet adhesion
vWF
Aggregation (hemostatic plug)
5
Endothelium
Basement membrane
Collagen

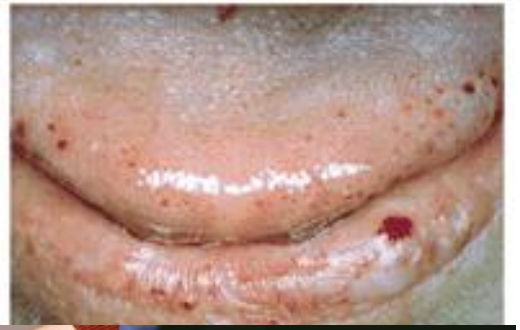

C. SECONDARY HEMOSTASIS
2 Phospholipid complex expression
3 Thrombin activation
4 Fibrin polymerization
1 Tissue factor
Tissue factor
1
Fibrin

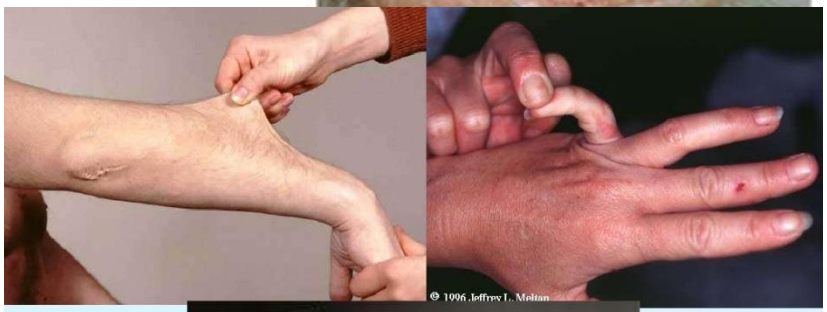

D. THROMBUS AND ANTITHROMBOTIC EVENTS
Release of:
• t-PA (fibrinolysis)
• thrombomodulin (blocks coagulation cascade)
Trapped neutrophil
Trapped red blood cells
Polymerized fibrin

CLASSIFICATION OF BLEEDING DISORDERS

1. Disorders of blood vessels
   - Hereditary hemorrhagic telengiectasy
   - Ehlers Danlos syndr.
   - Marfan syndr
   - Osteogenesis imperfecta
   - Homocysteinemia
   - Giant hemangiomas
   - Pseudoxantoma elasticum







2. Platelet disorders

3. Coagulation disorders

QUANTITATIVE PLATELET DISORDERS

A. Hyporegenerative (decreased production)

1. In assocation with bone marrow (BM) failure
   - Aplastic anemia
   - BM infiltration by leukemia, lymphoma and solid tumor
   - Chemotherapy, radiotherapy
   - Drugs and chemical
   - Infections (HIV, Parvovirus B19, bacteria)
2. Vit B12- Folic acid deficiencies
3. Congenital thrombocytopenia (TAR syndrome , Wiskott Aldrich syndrome)

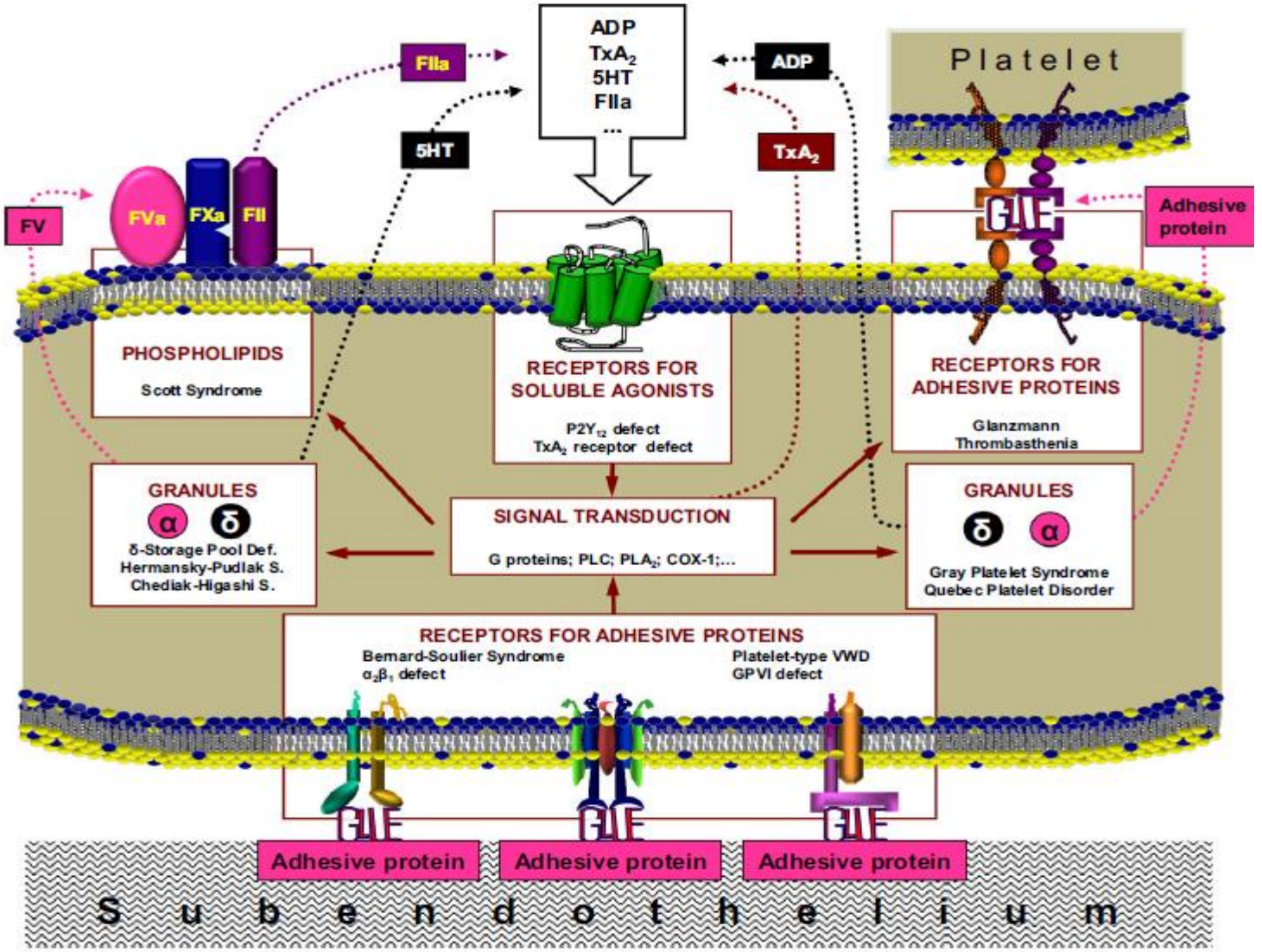
B. Decreased survival in peripheral blood

1. Immune mediated thrombocytopenias
   - Immune thrombocytopenic purpura (ITP)
   - Drug induced immune thrombocytopenias
   - Autoimmune disorders: SLE, autoimmune hemolytic anemia (Evans Syndrome)
   - Alloimmune thrombocytopenias

     Platelet alloimmunization due to recurrent platelet transfusion (anti-HLA antibodies)

     Fetal-neonatal alloimmune thrombocytopenia (due to anti PlA1 antibodies in pregnant women)
2. Non-immune mediated thrombocytopenia
   - Disseminated intravascular coagulation (DIC)
   - Hemolytic-Uremic Syndrome (HUS)
   - Giant hemangioma
   - Hypersplenism

QUALITATIVE PLATELET DISORDERS



Dovlatava N et al. BJH, 2015; 170: 150-161

Classification of coagulation disorders in children.

Inherited
Haemophilia A
Haemophilia B
von Willebrand disease
Deficiency of Factors II, V, VII, X, XI, XII or XIII
Dys-, hypo- or afibrinogenaemia
α-2 antiplasmin deficiency
Plasminogen activation inhibitor-1 deficiency
Acquired
Vitamin K deficiency
Liver disease
Disseminated intravascular coagulation
Massive transfusion syndrome
Dys- or hypo-fibrinogenaemia
Disorders associated with malignancy
Coagulation inhibitors

CLINICAL EVALUATION

- Careful personal history
  - ✓ Age
    - Fetal loss (neonatal alloimmune thrombocytopenia)
    - Large subcutaneous or intracranial bleedings
    - Bleeding from umblical stump (FXIII deficiency)
    - Subcutaneous or intramuscular bleeding after IM vaccination
    - Bruising when crawling starts
    - Hemartrosis when walking & running starts (hemophilia)
  - ✓ Gender (Predom. female in platelet disorders and predom. male in disorders of coagulation)
  - ✓ Medication
  - ✓ Family history

CLINICAL EVALUATION

- Characteristics of bleeding (immediately after trauma in platelet disorders, starts late-persists in disorders of coagulation)

- Type of bleeding

✓ Normal/abnormal bruising

  - Small bruises on bony prominences on the front of the body
  - Some bruising can be expected in all children from the time they begin to crawl (forehead, knees and shins)
  - In non-mobile infants - usually before the age of 9 months – significant bruising is unusual
  - Uncommon sites for bruising at all ages include the back, buttocks, arm and abdomen

✓ Considerable mucosal bleedings (epistaxis, gingival bleeding, menorrhagia)

✓ Bleedings after operations (circumsion, tooth extraction)

✓ Soft tissue, muscle and joint bleedings

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Evaluation of Pediatric Bleeding Questionnaire in Turkish Children With Von Willebrand Disease and Platelet Function Disorders

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Abstract

The diagnosis of mild bleeding disorders is not easy as most of the "healthy" individuals also report bleeding symptoms. In order to get a precise bleeding history, Pediatric Bleeding Questionnaire (PBQ) has been developed. In our study, Turkish children diagnosed with Von Willebrand disease (VWD), platelet function defect (PFD), and healthy children without any symptoms (control group 1) and healthy children with symptoms but found hemostatically normal (control group 2) were analyzed with PBQ. The cut off level for "positive bleeding score" was found to be ≥ 2 (area under the curve [AUC]: 0.785, 95% confidence interval [CI]: 0.718-0.852). The sensitivity, specificity, positive predictive value, and negative predictive value of PBQ to define VWD versus control group 1 was 100%, 97.4%, 96.4%, and 100%; VWD versus control group 2 was 100%, 53.1%, 64.3%, and 100%; PFD versus control group 1 was 93.3%, 53.1%, 73.7%, and 85%; and PFD versus control group 2 was 93.3%, 53.1%, 73.7%, and 85%, respectively.

Keywords

von Willebrand factor, platelet dysfunction, bleeding

Physical Examination

- Bleedings from mucosal surfaces or superficial cuts: disorders of primary hemostasis
- Hemarthrosis/ muscle bleedings: Hemophilia
- Bleeding from umblical stump in neonate: FXIII deficiency
- Hepatosplenomegaly, lymphadenopathy: leukemia
- Congenital malformations : syndromic macrothrombocytopenias

BLOOD SAMPLE COLLECTION

Pre-analytical errors

Problems with the tube

- Partially filled tubes
- Vacuum leak & citrate evaporation

Biological effects

- Hct≥55 or ≤ 15
- Lipemia, hyperbil., hemolysis

Problems with phlebotomy

Heparin contamination

Wrong label

Slow fill

Underfill

Vigorous shaking

Laboratory errors

Delay in testing

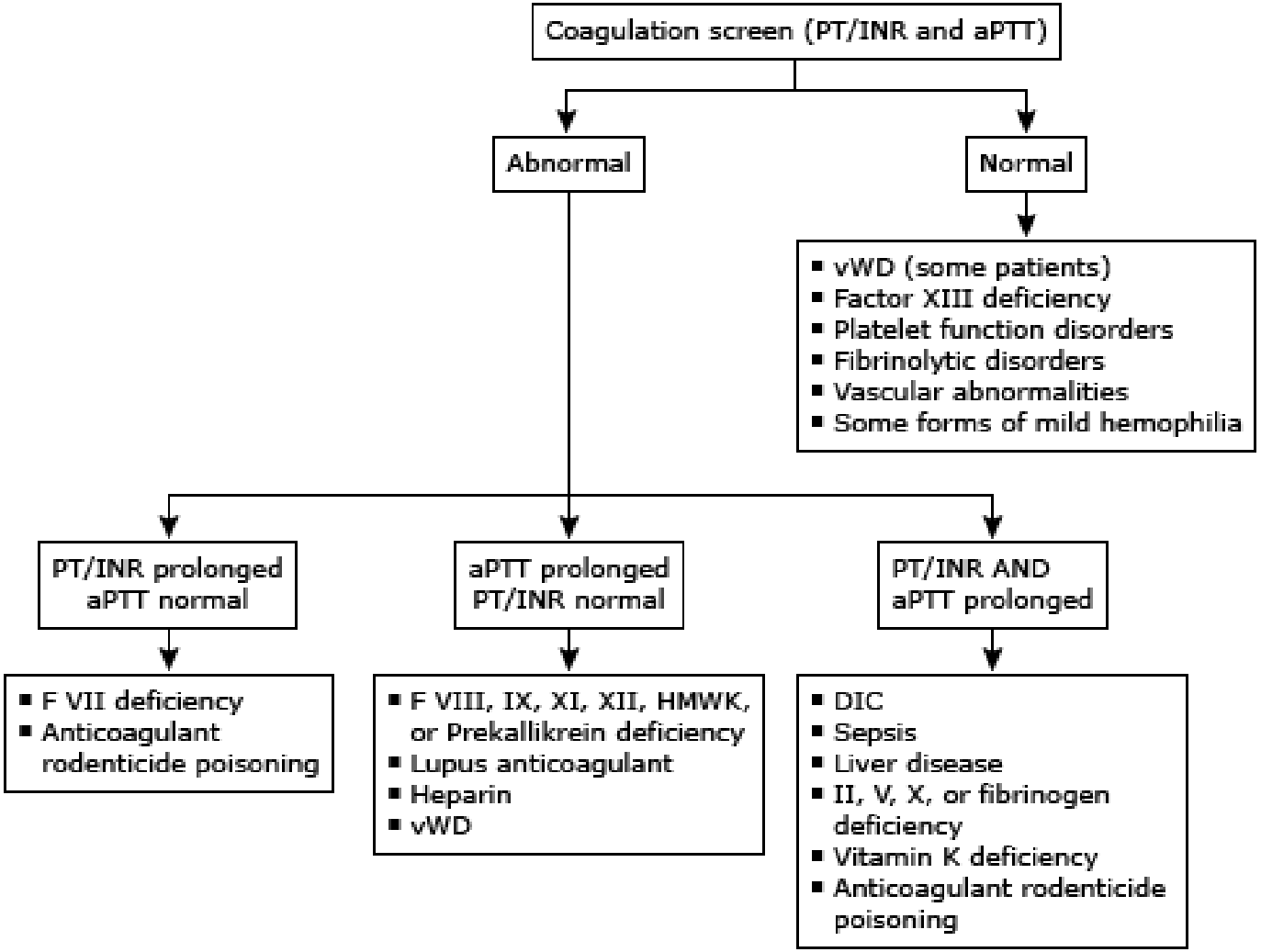
Prolonged incubation

Freeze and thaw deterioration

DIAGNOSTIC TESTS
Routine Screening

1. Platelet count and peripheral blood smear
2. PT, aPTT, fibrinogen level
3. Bleeding time and PFA-100
4. Hepatic and renal functions
5. FXIII screen
6. vWf antigen and activity (if there are mucosal bleedings)

Algorithm for evaluating children for disorders of hemostasis



NORMAL INITIAL COAGULATION TESTS

Table I. Haemostatic disorders which may present with normal coagulation screen and full blood count.

Mild von Willebrand disease
Mild haemophilia A or B
Mild factor XI or other single factor deficiency
Factor XIII deficiency
α-2 antiplasmin deficiency
Plasminogen activation inhibitor-1 deficiency
Glanzmann thrombasthenia
Platelet storage pool disease
Platelet release defect
Collagen disorders
Vitamin C deficiency

EXPECTED RESULTS OF SCREENING TESTS

Disorder	Platelet count	PT	aPTT	Fibrinogen
Vasculopathies, connective tissue diseases, or collagen disorders affecting skin	normal	normal	normal	normal or increased*
Thrombocytopenia	low	normal	normal	normal
Qualitative platelet abnormalities	normal or low¶	normal	normal	normal
Hemophilia A (factor VIII deficiency)	normal	normal	long	normal
von Willebrand disease	normalΔ	normal	normal or long◊	normal
Disseminated intravascular coagulation	low	long	long	low

Diagnostic Tests

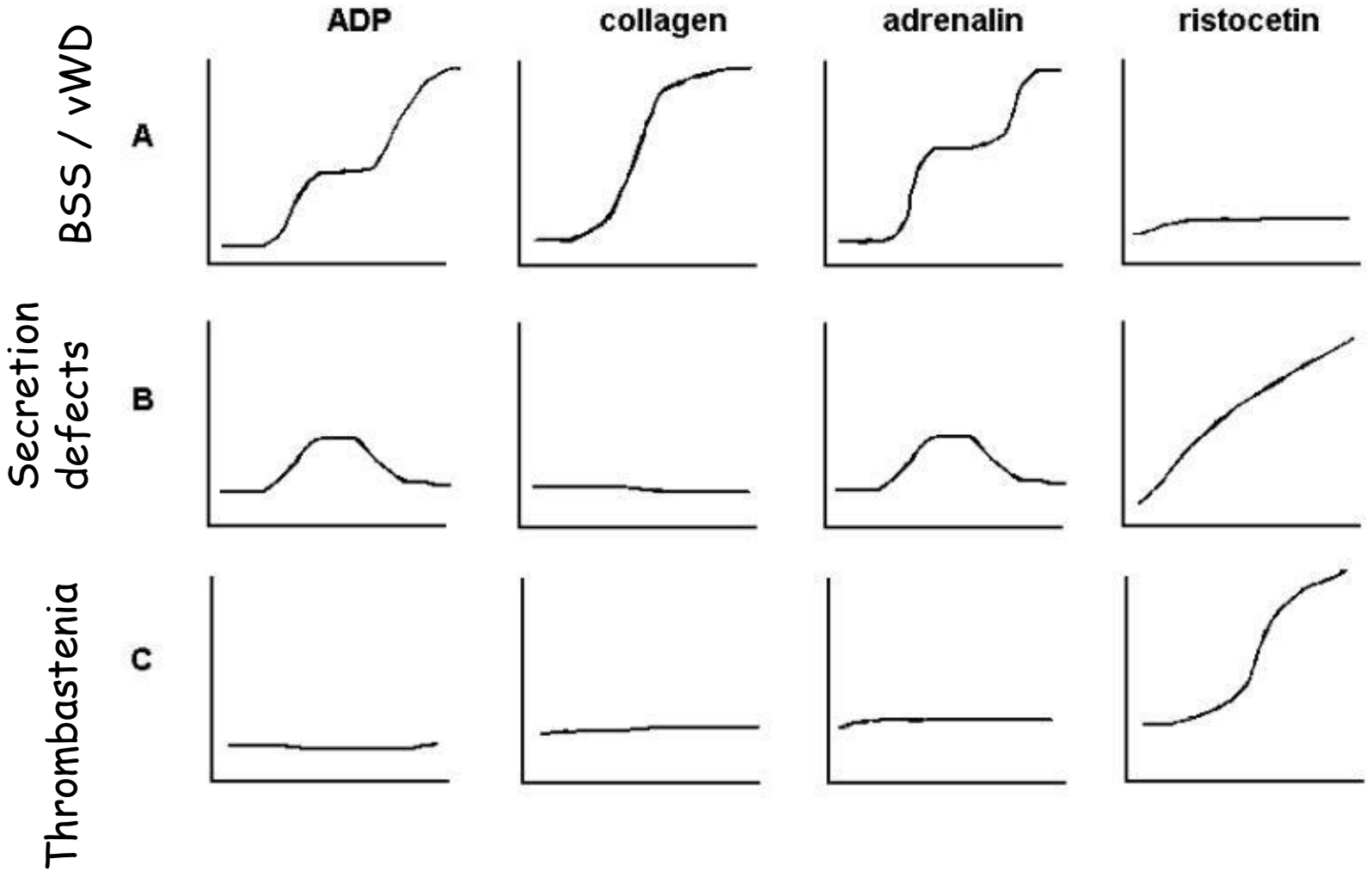
1. Measurement of clotting factors
2. vWf antigen and activity (if there are mucosal bleedings)
3. Platelet aggregation with ADP, collajen and ristocetin

- ATP/ADP release
- Genetic analysis

vWD CLASSIFICATION

	Type 1	Type 3	Type 2A	Type 2B*	Type 2M	Type 2N
vWF: Ag	↓	Absent	↓	↓	↓	Normal or ↓
vWF: Rco	↓	Absent	↓↓	↓↓	↓↓	Normal or ↓
FVIII	N	↓↓	N or ↓	N or ↓	N or ↓	↓↓
Multimer distribution	N	Absent	Loss HMWM	N	N	N

Platelet aggregation tracings in common platelet disorders and vWD



Principles of Management

Treat/prevent the bleeding, but not laboratory abnormality

- Avoid trauma
- Avoid using aspirin and other NSAI drugs
- Local hemostasis (first step in active bleeding)
  - Local pressure
  - Nasal packing (surgicel)
  - Antifibrinolytics- Tranexamic acid p.o (GIT bleedings, epistaxis, menorrhagia) or mouth wash
  - Fibrin sealants
  - Cold compress
  - Rest
  - Splint
  - Steroids

Therapeutic Materials

- Steroids
- IVIG
- Platelet concentrates
- DDAVP (mild-moderate hemophilia and type 1 and 2 vWD, uremia and cardiopulmonary by pass)-
  contraindicated in thrombosis and children below <2 years
- FFP: contains 0.8-1 U factor/ml
- Cryoprecipitate: contains FVIII, vWF, fibrinogen
- Factor concentrates
  - ✓ Plasma derived, lyophilized
  - ✓ Recombinant

Replacement of the Missing Hemostatic Component

1. On demand treatment: (to stop an active bleeding episode)
2. Prophylaxis: Regular injection of missing

clotting factors, 2-3 times in a week prevent joint disease in hemophilia, severe vWD and FX deficiency

- Inhibitor (antifactor antibody) development: 20 %

- Care cost in Hemophilia 50.000-80.000 $
- Care cost in Hemophilia with inhibitors 500.000 $

Factor Levels Required For Hemostasis

	(%)
Mild bleedings	10-20
Moderate bleedings	30-40
Severe bleedings	50-80
Major surgery	80-100
Life treatening bleedings	80-100

1U/kg FVIII increases blood FVIII level 2 %
1U/kg FIX increases blood FIX level 1 %

Novel Therapies

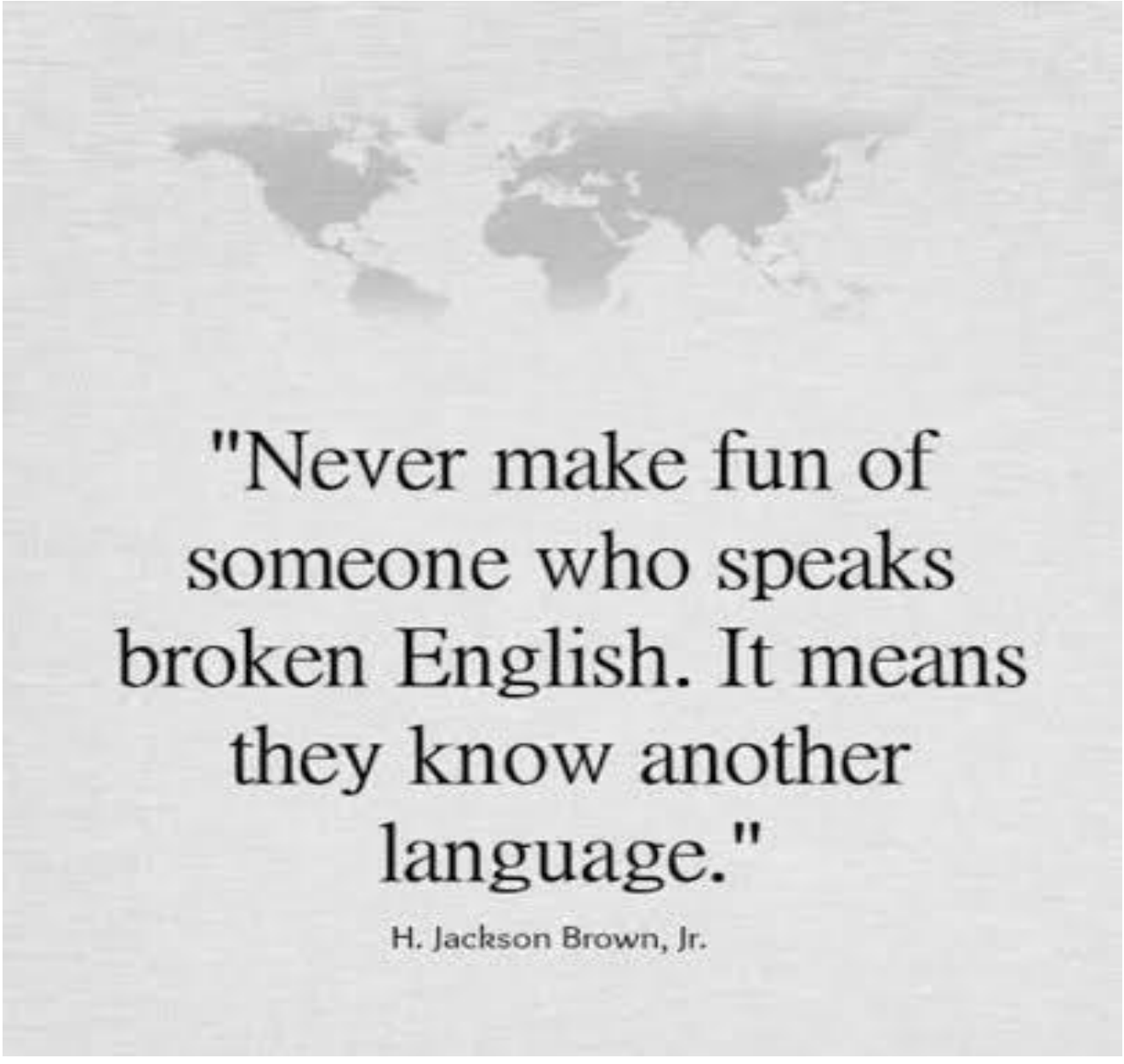
- Bone marrow transplantation from MSD- performed in a few cases with WAS and Glanzmann's thrombasthenia
- Gene therapy-clinical trials have given promising results in hemophilia B. Less succesful in hemophilia A and vWD

Prenatal Diagnosis

- The goal is to let the parents to have a healthy child with more proper care, education and social life possibilities

- DNA analysis in 9-11 weeks of gestation
- Fetal sex determination

Thank You


"Never make fun of someone who speaks broken English. It means they know another language."
H. Jackson Brown, Jr.