
بسم الله الرحمن الرحیم

OUTPATIENT DIAGNOSTIC APPROACH TO BLEEDING DISORDERS IN CHILDREN

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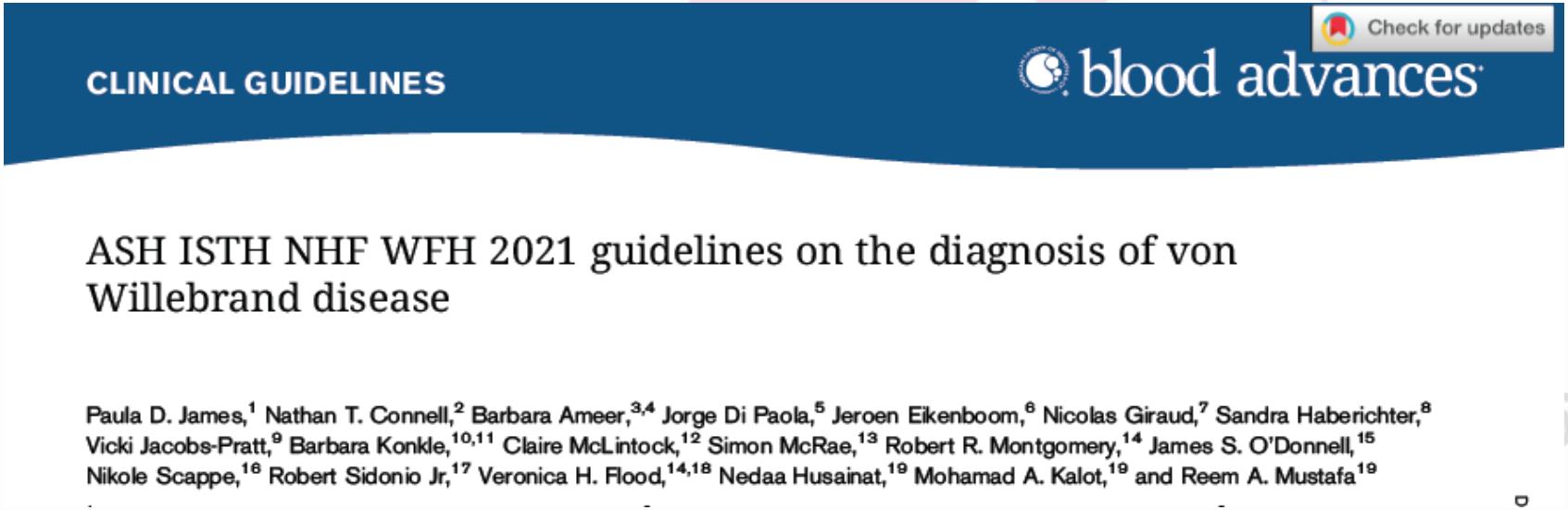
Refferences

- **SickKids Handbook of Pediatric Thrombosis and Hemostasis** 2nd, revised and extended edition
- http://www1.wfh.org/docs/en/Resources/Assessment_Tools_ISTHBAT.pdf.



CLINICAL GUIDELINES

blood advances

Check for updates

ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease

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Case

- 12 years old boy with recurrent epistaxis comes to your clinic
- No URI;
- No allergy
- No trauma or local problem
- Not related to seasons and climate conditions ,exercise, etc.
- Normal BP
- Laboratory evaluation :
  - Normal CBC & Platelet
  - BT=5`
  - PT=13`` PTT=40``

Main Problem

Prevalent complaint

- Easy bruising or bleeding ,especially in children remains a challenge for the consulting hematologist to define a “significant bleeding history” :
  - mild underlying defects such as type 1 VWD or platelet function defects

    OR
  - Normal population

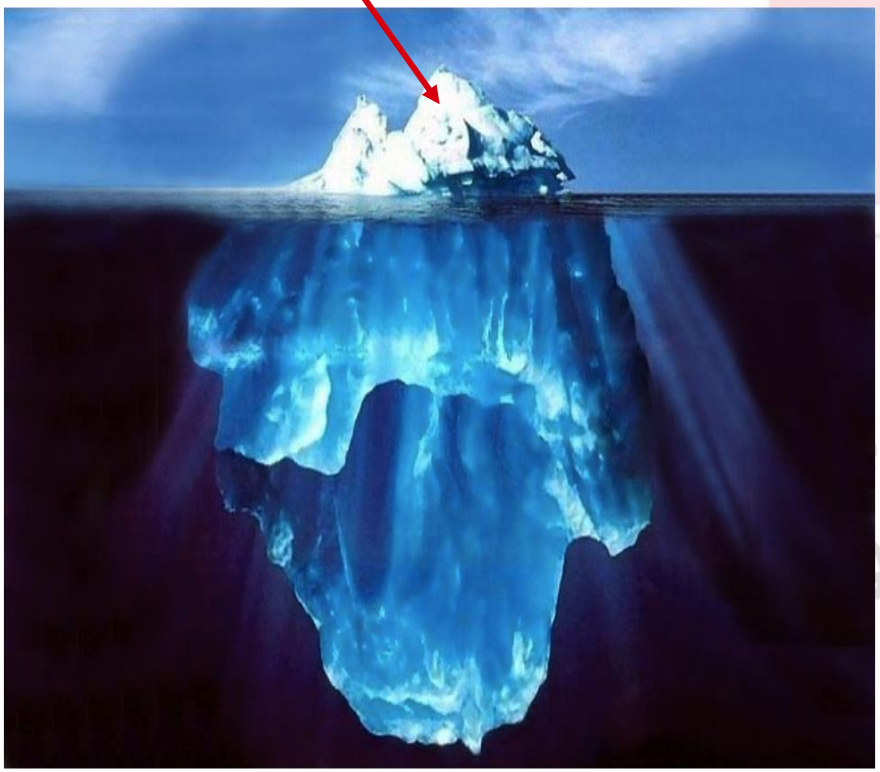
Limited Diagnostin tools

- the diagnostic limitations of available laboratory testing for mild bleeding disorders

Iceberg of VWD

Expected incidence in IRAN for :

- all types of VWD is about1/100
- bleeders is about 1/10000
- Sever bleeders is about 1/100000



Normal population

- Adults: (http://ds9.rockefeller.edu/RUBHPSR/; accessed May 1,2012)
  - 25% epistaxis,
  - 18% easy bruising,
  - 18% prolonged bleeding after a tooth extraction
  - 47% of women reported heavy menstrual bleeding.
- Children: (Nosek-Cenkowska B, et al.. *Thromb Haemost*. 1991;65(3):237-241).
  - 24% easy bruising
  - 39% epistaxis,

Other Questions

- To distinguish carriers in family members
- To select the type of requested special tests(VWD types ;Platelet function tests; other RBDs ;etc.)
- Treatment decision: the cases who need prophylaxis, intensified treatment, etc.

Key diagnostic tools

- (1) a carefully obtained bleeding history from the subject and close relatives, including sex, age, site and frequency of bleeding,DH, FH, details of consanguinity,etc
- (2) a detailed physical examination with a focus on the identification of physical findings that may provide important clues regarding an underlying diagnosis and
- (3) selected laboratory tests.

Clinical approach

1. **Is the bleeding significant ?**
2. **Local Vs Systemic ?**
3. **Platelet Vs Coagulation disorder ?**
4. **Inherited Vs Acquired ?**

The development of the Vicenza bleeding scores

Rodeghiero F, Castaman G, Tosetto A, et al. The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. *J Thromb Haemost*. 2005;3(12):2619-2626

Tosetto A, Rodeghiero F, Castaman G, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM- 1 VWD). J Thromb Haemost. 2006;4(4):766-773..

- Original Vicenza :study population included 42 type 1 VWD obligatory carriers and 215 control subjects
- Asked about a multitude of bleeding symptoms
- Scoring
  - Vicenza: from 0 to 3
  - European MCMDM-1VWD:-1 to 4
- 2 most predictive symptoms for the identification of VWD were
  - bleeding after tooth extraction or surgery
  - cutaneous bleeding (ecchymoses or hematomas).

Likelihood ratio for VWD using Vicensa BATs

Table 4. Diagnosis of von Willebrand's Disease Using the Bleeding Score

Bleeding score	*Likelihood ratio**	*Post-test probability (%)*
-3	0.00	0.0
-2	0.04	0.2
-1	0.10	0.5
0	0.13	0.7
1	1.60	8.0
2	2.20	10.0
3	3.00	13.0
4	16.00	43.0

NOTE: *This table is based on a 5 percent pretest probability.*

**—Likelihood ratio with a 95% confidence interval.*

Adapted with permission from Tosetto A, Rodeghiero F, Castaman G, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results for a multicenter European study (MCMDM-1 VWD). J Thromb Haemost. *2006;4(4):771.*

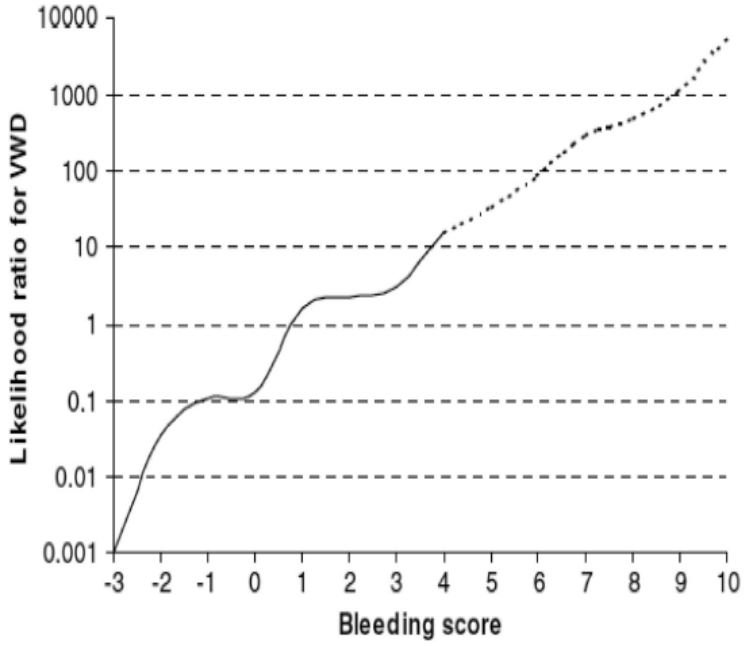


Figure 1. Likelihood ratios for VWD based on the Vicenza bleeding assessment tool (−1 version) and on data from the MCMDM-1 study. (Reprinted with permission from Tosetto et al.[15] Copyright 2007, Elsevier.)

CONDENSED MCMDM-1 VWD BAT

Condensed Molecular and Clinical Markers for the Diagnosis and Management of Type 1 (MCMDM-1) VWD Bleeding Questionnaire

Bowman M, et al . *J Thromb Haemost*. 2008;6(12):2062-2066

- 6-page questionnaire that requires 5-10 minutes (in comparaison with 40 minutes for 17 pages)

The Pediatric Bleeding Questionnaire (PBQ) of MCMDM-1 VWD BAT

Bowman M,et al. *J Thromb Haemost*. 2009;7(8):1418-1421.

- Shorter life experience, children have fewer or no exposures to bleeding challenges
- Added “other” category,which has pediatric-specific bleeding symptoms toMCMDM-1 (such as umbilical stump bleeding, cephalohematoma, postcircumcision bleedingetc.)

The ISTH/SSC Bleeding Assessment Tool

- Developed by members of an ISTH/SSC Joint VWF and Perinatal/Pediatric Hemostasis Subcommittee Working Group since 2010
- **used in children and adults to diagnose mild bleeding disorders** in patients who are being evaluated for a bleeding disorder **for the first time**
- Only symptoms reported before and at the time of diagnosis should be included'
- **Overall utility: R/O VWD , Possible Platelet dysfunction**
- **Limitations: few validation studies,** Requires a skilled professional to administer and 20 minutes
- An abnormal ISTHBAT BS for children (male or female) is ≥ 3.

Symptom	0[1]	1[1]	2	3	4
Epistaxis	No/trivial	>5/year	Consultation	Packing, cauterization, or	Blood transfusion or replacement
Oral cavity	No/trivial	Present	Consultation	Surgical hemostasis or	Blood transfusion, replacement
	done	intervention	procedures, no intervention[3]		

✓R/O other local or systemic causes: seasonal occurrence , URI, Dusty dry air, High BP , etc.

- Consultation only: the patient sought medical evaluation and was either referred to a specialist or offered detailed laboratory investigation

✓ petechiae when adequately described by the patient or relatives; or
✓hematomas when occurring without trauma.

➢ **tooth eruption : when requires assistance** or supervision by a physician, or lasts at least **10 minutes**
➢**bites to lip and tongue,:** at least **10 minutes** or causes a **swollen tongue or mouth**.

➢Permanent teeth
➢occurring after leaving the dentist's office and requiring a new, unscheduled visit

PBQ:

➢Any report of bleeding stopped
- ➢without consultation : 1
- ➢With consultaion only:2

Pediatric Bleeding Questionnaire (PBQ)

Score / Symptom	-1	0	1	2	3	4
Epistaxis	-	No or trivial (≤5 per year)	>5 per year OR >10 minutes duration	Consultation only	Packing, cauterization or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Cutaneous	-	No or trivial (≤1cm)	>1cm AND no trauma	Consultation only	-	-
Minor wounds	-	No or trivial (≤5 per year)	>5 per year OR >5 minutes duration	Consultation only or Steri-strips	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Oral cavity	-	No	Reported at least once	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Gastrointestinal tract	-	No	Identified cause	Consultation or spontaneous	Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	-
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing, repacking or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Menorrhagia	-	No	Reported or consultation only	Antifibrinolytics or contraceptive pill use	D&C or iron therapy	Blood transfusion, replacement therapy, desmopressin or hysterectomy
Post-partum	No bleeding in at least 2 deliveries	No deliveries or no bleeding in 1 delivery	Reported or consultation only	D&C, iron therapy or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin	-
Muscle hematoma	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system	-	Never	-	-	Subdural, any intervention	Intracerebral, any intervention
Other [a]	-	No	Reported	Consultation only	Surgical hemostasis, antifibrinolytics or iron therapy	Blood transfusion, replacement therapy or desmopressin

Symptom	0[1]	1[1]	2	3	4
Muscle hematomas	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
CNS bleeding	Never	–	–	Subdural, any intervention	Intracerebral, any intervention
Other bleedings[5]	No/trivial	Present	Consultation only[2]	Surgical hemostasis, antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin

- Include: umbilical stump bleeding, cephalohematoma, cheek hematoma caused by sucking during breast/bottle feeding, conjunctival hemorrhage, or excessive bleeding following circumcision or venipuncture.
- Spontanous or Repeated abortion(?)
- Delayed wound healing (?)
- Their presence in infancy requires detailed investigation independently from the overall score.

Menorrhagia points(ISTH-BAT)

- Severity : more than 80 ml/period
  - More than 30 of tampons/pads used for a typical menstrual cycle
  - Hourly (0.5–2.0 h) change of tampon/pad on the heaviest day of menstrual period
  - use a tampon and a pad at the same time OR a super-absorbent tampon or pad
  - Clot >1 cm or flooding
  - frequently stain through clothes during menses
  - pictorial blood loss assessment chart (PBAC) >100
- Duration: More than 7 days ; Present since menarche and > 12 months
- Needs to treatment : OCP; Antifibrinolytics;DDAVP; anaemic or low in iron;Transfusion;surgical intervention
- lost time from work or school ≥ 2 times in the past year because of heavy periods

Continue:

- Postpartum hemorrhage

✓ uterine discharge (lochia) that lasts for more than 6 weeks

✓ judged by the obstetrician as abnormally heavy or prolonged

✓ Frequency

✓ Needs to treatment

Menorrhagia	No/trivial	Consultation only[2] or Changing pads more frequently than every 2 h or Clot and flooding or PBAC score >100[4]	Time off work/ school >2/year or Requiring antifibrinolytics or hormonal or iron therapy	Requiring combined treatment with antifibrinolytics and hormonal therapy or Present since menarche and >12 months	Acute menorrhagia requiring hospital admission and emergency treatment or Requiring blood transfusion, replacement therapy, desmopressin or Requiring dilatation and curettage or endometrial ablation or hysterectomy
Postpartum hemorrhage	No/trivial or no deliveries	Consultation only[2] or Use of syntocin or Lochia >6 weeks	Iron therapy or Antifibrinolytics	Requiring blood transfusion, replacement therapy, desmopressin or Requiring examination under anesthesia and/or the use of uterine balloon/package to tamponade the uterus	Any procedure requiring critical care or surgical intervention (e.g. hysterectomy, internal iliac artery legation, uterine artery embolization, uterine brace sutures)

Symptom-specific bleeding scores for menorrhagia (Pictorial Blood Loss Assessment Chart) and epistaxis are useful for describing the severity of the specific bleeding symptom

Pictorial Blood loss Assessment Chart (PBAC)

Menstrual chart and scoring system

Date of start ☐ ☐ ☐ Score ☐

day month year

Towel	1	2	3	4	5	6	7	8
								
								
								
Clots/flooding *Clots: size*								

Tampon	1	2	3	4	5	6	7	8
								
								
								
Clots/flooding *Clots: size*								

A score ≥ 100 has a sensitivity and specificity for a diagnosis of menorrhagia of ≥ 80%,

Scoring system

Towels

1 point for each lightly stained towel

5 points for each moderately soiled towel

wel is
ed with

1 point for each lightly stained tampon

5 points for each moderately soiled tampon

10 points if the tampon is completely saturated with blood

Clots

1 point for small clots

5 points for large clots

Source: U.K. Haemophilia Society, A Guide for Women Living with von Willebrand's

Table 2. Epistaxis scoring system [9]

Component	Score[1]
Frequency	
5–15/year	0
16–25/year	1
>25/year	2
Duration	
<5 min	0
15–30 ml	1
>30 ml	2
Epistaxis history/age[3]	
<33%	0
33–67%	1
>67%	2
Site	
Unilateral	0
Bilateral	2

- Sum of scores for all components: mild = 0–6; severe = 7–10
- Estimation of average blood loss per episode, based on fractions or multiples of teaspoons, tablespoons, or cups.
- Proportio of the child's life that nosebleeds have been recurrent (>5/year).

Other points

- **A positive family history** increases the risk of a bleeding disorder
- Circumcision (with cutting methods) and ear ring replacement as a haemostatic challenge ?
- History of Renal, Liver or Hematological disease
- Drug history
- Distinction between 0 and 1 is of critical importance

Pre-operative recommendations

- The European Society of Anaesthesiology :
  - specifically recommends the use of a structured patient interview or questionnaire **before surgery or invasive procedures**.
- The British Committee for Standards in Haematology:
  - recommends a bleeding history be taken in **all patients preoperatively and prior to invasive procedures**
- Bleeding history may be **negative in paediatric patients** due to lack of haemostatic challenges. Therefore, if a **positive family history exists**, some laboratory workup will be required to confirm or exclude a bleeding disorder

- 1. Chee YL, Crawford JC, Watson HG and Greaves M. Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. British Committee for Standards in Haematology. British Journal of Haematology, 2008;140:496–504.
- 2. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2013;30:270-382.

Drug History

Table 5. Medications That Cause Bleeding and Bruising

Common

Aspirin
Clopidogrel (Plavix)
Heparin
Nonsteroidal anti-inflammatory drugs
Warfarin (Coumadin)

Rare

Cephalosporins
Ginkgo biloba
Gold
Interferon
Metaxalone (Skelaxin)
Penicillins
Propothiouricil
Selective serotonin reuptake inhibitors
Testosterone replacement
Tricyclic antidepressants

Drugs Proved or Suspected to Induce Drug-Dependent Antibody- Mediated Immune Thrombocytopenia

Anti-inflammatory
- Acetaminophen
- Acetylsalicylic acid
- Diclofenac
- Ibuprofen
- Indomethacin
- Meclofenamate
- Mefenamic acid
- Naproxen
- Oxyphenbutazone
- Phenylbutazone
- Piroxicam
- Sodium-p-amino salicylic acid
- Sulfasalzine
- Sulindac
- Tolmetin

Antibiotics
- *Antituberculous* drugs
  - Ethambutol
  - Isoniazid
  - Para-aminosalicylic acid (PAS)
  - Rifampin
  - Streptomycin
- Penicillin group
  - Ampicillin
  - Methicillin
  - Penicillin
  - Mezlocillin
  - Piperacillin
- Cephalosporin
  - Cefamandole
  - Cefotetan
  - Ceftazidime
  - Cephalothin
- Sulfonamides
  - Sulfamethoxazole
  - Sulfamethoxypyridazine
  - Sulfisoxazole
- Other antibiotics
  - Amphotericin B
  - Ciprofloxacin
  - Clarithromycin
  - Fluconazole
  - Gentamicin
  - Indinavir
  - Nalidixic acid
  - Novobiocin
  - Pentamidine
  - Sodium Stibogluconate
  - Stibophen
  - Suramin
  - Vancomycin

Antineoplastic
- Actinomycin-D
- Aminoglutethimide
- Tamoxifen

Anticonvulsants, sedatives, and antidepressants
- Amitriptyline
- Carbamazepine
- Desipramine
- Diazepam
- Doxepin
- Haloperidol
- Imipramine
- Lithium
- Mianserin
- Phenytoin
- Valproic acid

Cardiac and antihypertensive drugs
- Acetazolamide
- Amiodarone
- Alprenolol
- Captopril
- Chlorothiazide
- Chlorthalidone
- Digoxin
- Digitoxin
- Furosemide
- Hydrochlorothiazide
- α-methyldopa
- Oxprenolol
- Procainamide
- Spironolactone

H2-antagonists
- Cimetidine
- Ranitidine

Cinchona alkaloids
- Quinidine
- Quinine

Miscellaneous
- Antazoline
- Chlorpheniramine
- Chlorpropamide
- Danazol
- Desferrioxamine
- Diethylstilbestrol
- Etretinate
- Glibenclamide
- Gold salts
- Heparin
- Interferon-α
- Iodinated contrast agents
- Isotretinoin
- Minoxidil
- Levamisole
- Lidocaine
- Morphine
- Papaverine
- Ticlopidine

Foods
- Beans

Thrombosis Research 148 (2016) 128–134

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Establishment of a bleeding score as a diagnostic tool for patients with rare bleeding disorders

Roberta Palla [a,*], Simona M. Siboni [b], Marzia Menegatti [a], Khaled M Musallam [b], Flora Peyvandi [a,b], on behalf of the European Network of Rare Bleeding Disorders (EN-RBD) group

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Platelet Vs Coagulation disorder

Symptom	Platelet	Coagulation
Petechiae	Yes	No
Sites	Skin & Mucosa	Deep Tissue
Time	Immediate	Delayed
Ecchymoses /Hematomas	Yes	Yes

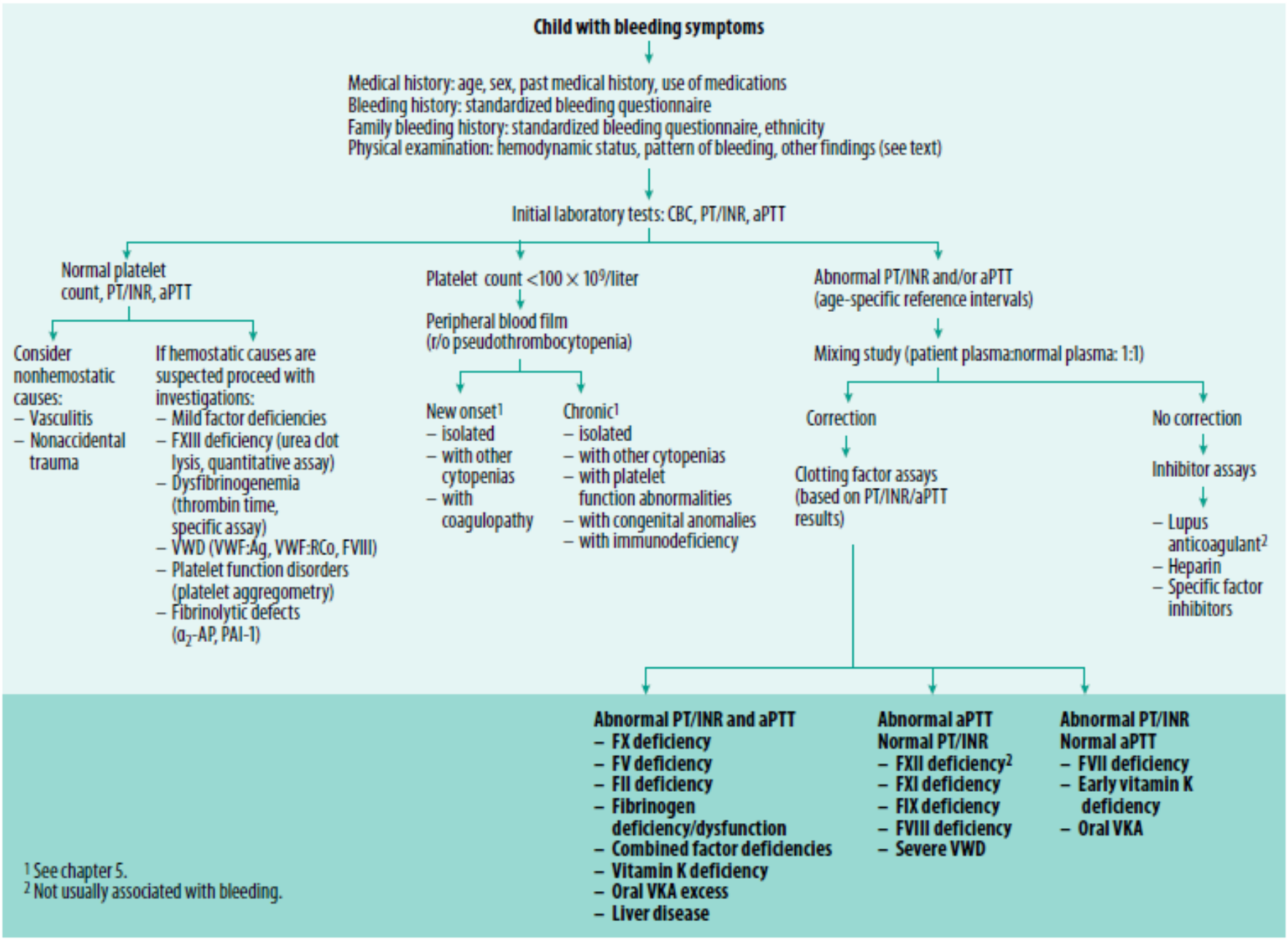
Note: Local pressure is effective in platelet bleeding but not in coagulation dis.

Table 1. Clinical abnormalities associated with inherited bleeding disorders

Coagulation disorders	
FXIII deficiency	poor wound healing, severe scar formation
Platelet function defects	
Hermansky-Pudlak syndrome	oculocutaneous albinism
Chediak-Higashi syndrome	oculocutaneous albinism, infections, neutrophil peroxidase-positive inclusions
ARC syndrome	arthrogryposis, renal dysfunction, cholestasis
MYH9-related disease	cataracts, sensorineural hearing defect, nephritis
Leukocyte adhesion deficiency type III	recurrent severe infections, delayed separation of the umbilical cord, neutrophilia
Thrombocytopenia	
Wiskott-Aldrich syndrome	eczema, immunodeficiency
Thrombocytopenia with absent radii, amegakaryocytic thrombocytopenia with radioulnar synostosis	skeletal defects
DiGeorge/velocardiofacial syndrome	cleft palate, cardiac defects, facial anomalies, learning disabilities
Paris-Trousseau/Jacobsen syndrome	cardiac defects, craniofacial anomalies, mental retardation
X-linked thrombocytopenia and dyserythropoiesis with or without anemia/X-linked thrombocytopenia-thalassemia	microcytosis of RBCs, unbalanced hemoglobin chain synthesis resembling β-thalassemia minor

Laboratory Approach

1. **Demonstration of the defect**
2. **Identification of the defect(s)**
3. **Assessment of severity**
4. **Consequential studies eg. carrier detection**
5. **Monitoring of treatment**



[1] See chapter 5.
[2] Not usually associated with bleeding.

Screening Tests

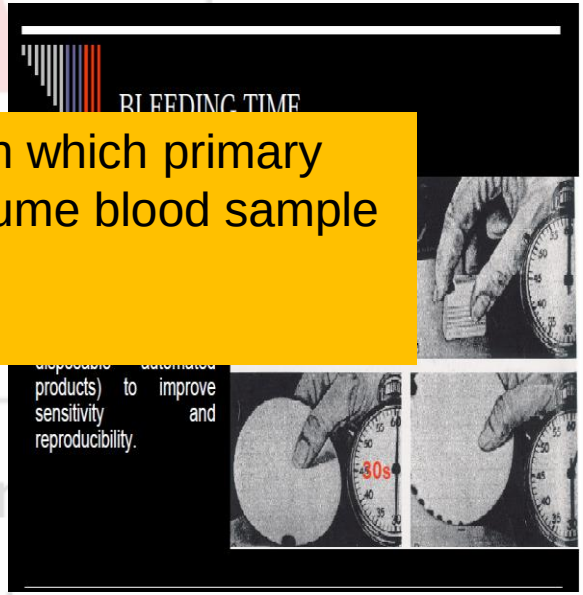
1. Platelet count & morphology
2. Bleeding Time
3. Clotting Time?
4. Prothrombin Time
5. Activated Partial Thromboplastin Time
6. Thrombin Time
7. Clot lysis test

Bleeding time
(Ivy Method)

- Inflate and Fix the pressure cuf on arm at 40 mmHg
- make a horizontal incision (1mm depth, 5 mm length) on volar surface of the forearm;2 inches below the elbow line
- dry the bleeding border with drying paper every 30 Sec.
- No

PFA-100 ® and recently *PFA-200* ® *are* instruments in which primary platelet-related hemostasis is simulated with small volume blood sample

Not available yet in Iran



❖ B

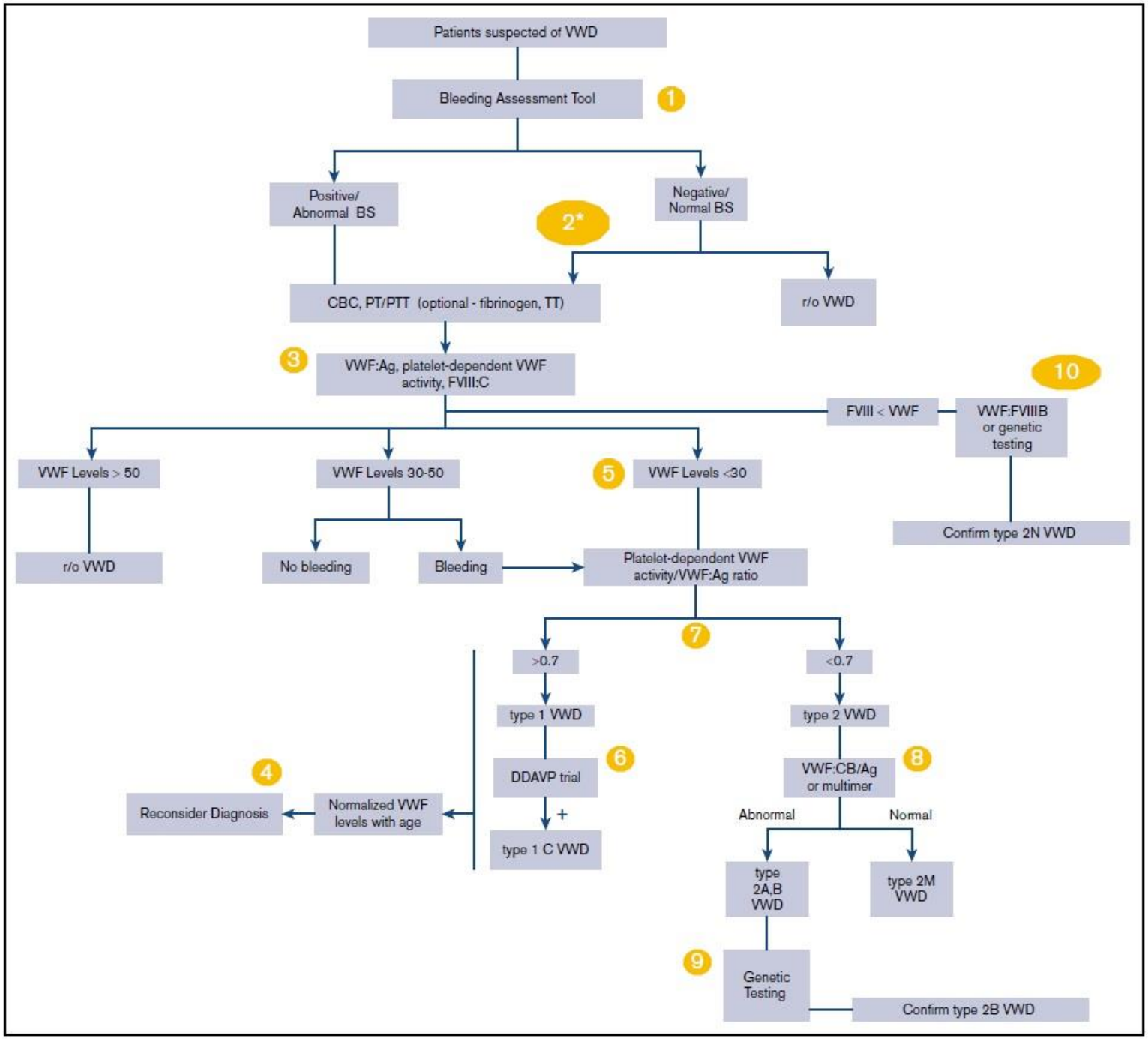
✓ platelet count less than 80000-100000 (some times less than 40000 in acute ITP)

✓ Platelet dysfunction Dis.

- Medication
- Azotemia
- VWD
- Platelet aggregation

Collection of blood sample

1. Minimum circulatory stasis
2. Clean venous puncture
3. Proper anticoagulant
4. Proportion of blood to anticoagulant
5. Separation of plasma and storage
6. Effect of stress, pregnancy, drugs
7. Effect of PCV on the proportion of plasma to anticoagulant


Patients suspected of VWD
Bleeding Assessment Tool
1
Positive/ Abnormal BS
Negative/ Normal BS
2*
CBC, PT/PTT (optional - fibrinogen, TT)
r/o VWD
3
VWF:Ag, platelet-dependent VWF activity, FVIII:C
10
FVIII < VWF
VWF:FVIIIB or genetic testing
Confirm type 2N VWD
VWF Levels > 50
VWF Levels 30-50
5
VWF Levels <30
r/o VWD
No bleeding
Bleeding
Platelet-dependent VWF activity/VWF:Ag ratio
7
>0.7
<0.7
type 1 VWD
type 2 VWD
6
DDAVP trial
+
type 1 C VWD
8
VWF:CB/Ag or multimer
4
Reconsider Diagnosis
Normalized VWF levels with age
Abnormal
Normal
type 2A,B VWD
type 2M VWD
9
Genetic Testing
Confirm type 2B VWD

Laboratory Values for VWD*

Condition	Description	VWF:RCo (IU/dL)	VWF:Ag (IU/dL)	FVIII	VWF:RCo/ VWF:Ag Ratio
Type 1	Partial quantitative VWF deficiency	<30**	<30**	Low or Normal	>0.5-0.7
Type 2A	Decreased VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers	<30**	<30-200**	Low or Normal	<0.5-0.7
Type 2B	Increased affinity for platelet GPIb; decreased platelets	<30**	<30-200**	Low or Normal	Usually <0.5-0.7
Type 2M	Decreased VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers	<30**	<30-200**	Low or Normal	<0.5-0.7
Type 2N	Markedly decreased binding affinity for FVIII	30-200	30-200	Very Low	>0.5-0.7
Type 3	Virtually complete deficiency of VWF	<3	<3	Extremely Low (<10 IU/dL)	Not applicable
"Low VWF"**		30-50	30-50	Normal	>0.5-0.7
Normal		50-200	50-200	Normal	>0.5-0.7

*These values represent prototypical cases. Exceptions occur, and repeat testing may be necessary.

**<30 IU/dL is designated as the level for a definitive diagnosis of VWD; some patients with type 1 or type 2 VWD have levels of VWF:RCo and/or VWF:Ag of 30-50 IU/dL.

NOTE: 30 IU/dL is recommended as the "cut-off" for the definite diagnosis of VWD for the following reasons: 1) high frequency of blood type O in the United States, which is associated with "low" VWF levels; 2) bleeding symptoms are reported by a significant proportion of normal individuals; 3) no abnormality in the VWF gene has been identified in many individuals who have mildly to moderately low VWF:RCo levels. This does not preclude the use of agents to increase VWF levels in those who have VWF:RCo of 30-50 IU/dL and who may be at risk for bleeding.

For patients with an abnormal initial VWD screen (low VWF:Ag and/or platelet-dependent VWF activity) suspected of type 1 VWD, should the diagnostic cutoff be at VWF:Ag and/or VWF platelet-dependent activity <0.30 IU/mL or <0.50 IU/mL?

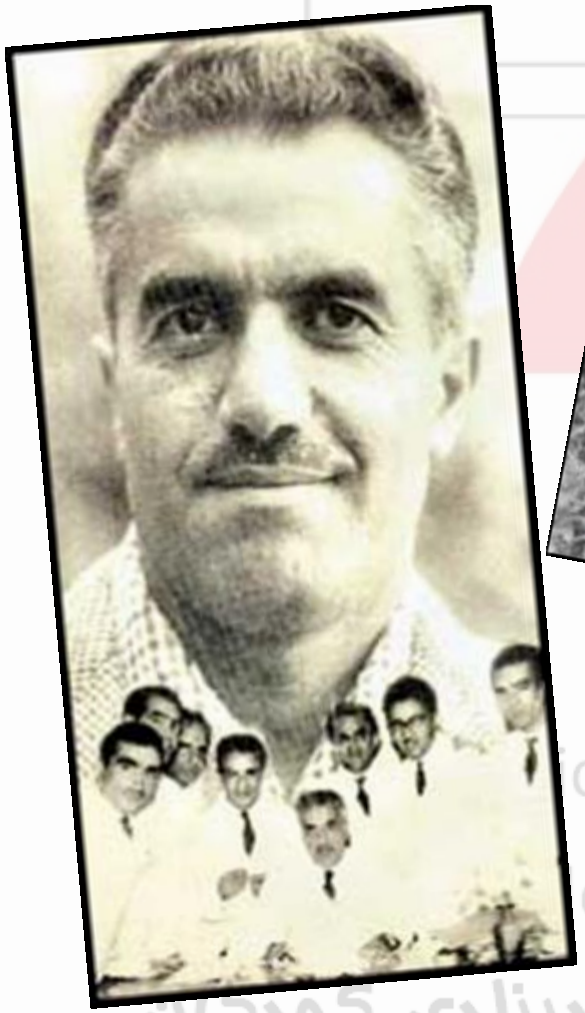
Recommendation 6

The panel *recommends* a VWF level of <0.30 IU/mL regardless of bleeding, and for patients with abnormal bleeding, a VWF level of <0.50 IU/mL to confirm the diagnosis of type 1 VWD (strong recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Remarks:

- VWF level(s) refers to VWF:Ag and/or platelet-dependent VWF activity (eg, VWF:GPIbM).
- The lower limit of the normal range as determined by the local laboratory should be used if it is <0.50 IU/mL. ABO-specific reference ranges are not required.
- VWF is an acute-phase reactant that increases in response to a variety of stimuli (eg, bleed, trauma, pregnancy). VWD diagnostic testing should be performed when patients are at a baseline state of health.

- **Basic tests:**
  - Bleeding time
  - CBC;platelet
  - Prothrombin time(PT) & mixing test
  - Activated partial thromboplastin time (aPTT) & mixing test
  - BG
- **1st specific VWD diagnostic tests:**
  - Factor VIII clotting activity
  - vWF:Ag
  - vWF platelet dependent activity: GP1bM; Ristocetin cofactor activity
- **2nd specific VWD diagnostic tests:**
  - Collagen binding activity
  - F VIII binding activity
  - vWF: pp
  - LD-RIPA
  - Multimeric analysis (to define the type of VWD)
- **Other coagulation factor deficiency`s diagnostic tests:**
  - Coagulation factor assay (one stage;chromogenic assay)
  - Clot lysis test ; Elisa ;etc.
- **Platelet function assay & diagnostic tests:**
  - RIPA
  - Platelet aggregation tests
  - Platelet secretion tests
  - FCM: CD41/61 ; CD 42
- **Genetic tests**



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