
بنام خداوند جان و خرد

Bleeding Disorders of Unknown Cause

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Case Presentation

01 Patient Introduction

Age: 44 years old, Gender: Female, Location: Shiraz

Initial Refer to IBTO: At age 30

Menstrual History:

- Menarche at age 12, regular cycles, 3 days duration with no significant bleeding
- At age 30, presented with menorrhagia and passage of clots
- Experienced two episodes of HMB for more than 2 weeks, requiring FFP transfusion

Case Presentation

02

Clinical Symptoms and History

Spontaneous Bruising (Ecchymosis):
- Mild bruising on upper and lower limbs, not severe but noticed since early 20s
- Ecchymosis score: 2

Epistaxis:
- Spontaneous nosebleeds occurring up to twice a week, self-resolving without medical intervention
- Epistaxis score: 2

Gum Bleeding (Gingival Bleeding):
- Self-resolving gum bleeding, occurring with brushing since age 26
- Teeth discoloration, one tooth extraction at age 32
- Gingival bleeding score: 2

Delayed Healing of Minor Cuts:
- Delayed wound healing, requiring more than 5 incidents per year
- Delayed healing score: 1

Case Presentation

03

Medical History and Surgeries

Cholecystectomy at age 22:
- Required blood transfusion in the operating room
- 45 days post-surgery, developed abdominal swelling and pain, later ERCP done
- Result: Normal pancreas, but experienced bleeding, requiring sclerotherapy

Spontaneous Hematoma in Left Leg (Age 28):
- Swelling, pain, and significant bruising in the left leg
- Suspected DVT, but negative doppler ultrasound
- No anticoagulation given, resolved spontaneously
- Hematoma score: 2

First Pregnancy (Age 21):
- Cesarean section delivery
- No significant bleeding complications during or after delivery

Second Pregnancy (Age 38):
- Cesarean section delivery
- Prophylactic plasma transfusion given prior to surgery due to bleeding tendency

Case Presentation

05

Bleeding Score=15

Menorrhagia: Score 4 (Heavy bleeding with clot passage, requiring FFP)

Epistaxis: Score 2 (Frequent spontaneous nosebleeds)

Gum Bleeding: Score 2 (Bleeding after brushing)

Delayed Healing of Cuts: Score 1 (Minor cuts take longer to heal)

Post-surgical Bleeding: Score 4 (Post-cholecystectomy bleeding requiring sclerotherapy)

Spontaneous Bruising (Ecchymosis): Score 2 (Mild bruising, recurrent

Case Presentation

06

Family and Genetic History

Family History:

- No known family members with bleeding disorders
- Siblings have normal bleeding patterns
- The parents were distantly related

Case Presentation

07

Clinical and Surgical History

Childbirth History:

- Age 21: First cesarean section with no significant bleeding
- Age 38: Second cesarean section with prophylactic plasma
- Menstrual History: Normal bleeding for daughter

Dental and Surgical Procedures:

- Required prophylactic FFP before dental work due to bleeding risk
- Allergic reactions to FFP made further transfusions problematic

Step 1:

- **PT (P)** = 12.5, **PT (N)** = 11
- **PTT (P)** = 30, **PTT (C)** = 31
- **BT= 2**

Step 2:

- **Factor XI**: 132, **Factor VIII**: 126, **Factor IX**: 172,
- **VWF:Ag** : 72, **(VWF:RCo)**: 90, **VWF:IBR**: 62

Step 3:

Factor VII: 81, **Factor X**: 113, **Factor II**: 103,
Factor V: 82, **Fibrinogen (Fg)**: 384, **Plt agg**: NL
Platelet ATP release: Normal (NL)

Step 4:

- **α_2 antiplasmin = 123**
- **Factor XIII**: 172

Case Presentation

The patient requires dental care management while balancing bleeding risk and allergic reactions to FFP, which requires finding alternative prophylactic treatments.

Mild Bleeding Disorders

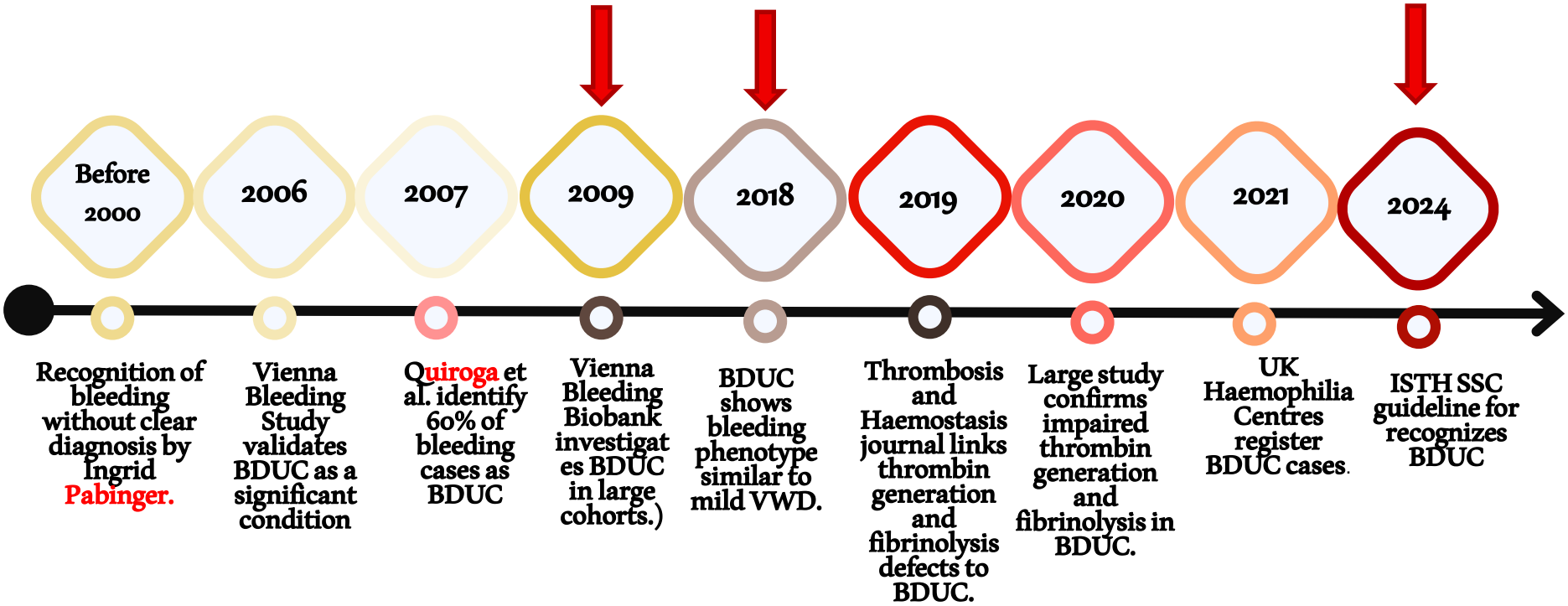
- A broad spectrum of mild to moderate **bleeding symptoms**:
  I. Mucocutaneous bleeding: epistaxis, easy bruising, hematomas, HMB
  II. Hemorrhagic events following surgical procedures, tooth extractions, or childbirth.

- Despite extensive investigations, only **30% to 40%** of patients diagnosed with a **recognized MBD** such as VWD, mild hemophilia (FVIII, FIX, or FXI deficiency) or IPFD

Bleeding Disorder of Unknown Cause (BDUC):

- **Standardized Definition**
- **Diagnostic Pathway**
- **Practical Management**

BDUC Timeline



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ISTH SSC COMMUNICATION

Standardization of definition and management for bleeding disorder of unknown cause: communication from the SSC of the ISTH

Ross I. Baker[1,2,3,4] | Philip Choi[5,6] | Nicola Curry[7,8] | Johanna Gebhart[9] | Keith Gomez[10] | Yvonne Henskens[11,12] | Floor Heubel-Moenen[13] | Paula James[14] | Rezan Abdul Kadir[15,16] | Peter Kouides[17] | Michelle Lavin[4,18,19] | Marie Lordkipanidze[20,21] | Gillian Lowe[22] | Andrew Mumford[23] | Nicola Mutch[24,25] | Michael Nagler[26,27] | Maha Othman[28,29,30] | Ingrid Pabinger[9] | Robert Sidonio[31] | Will Thomas[32] | James S. O'Donnell[4,18,19] | on behalf of the ISTH SSC Von Willebrand Factor, Platelet Physiology, and Women's Health Issues in Thrombosis and Haemostasis

Standardized Definition

(ISTH SSC 2024)

ISTH SSC recommendation:

Use the term "Bleeding Disorder of Unknown Cause (BDUC)" for patients with:

I. **Clinically significant bleeding phenotype (objectively assessed), AND**

II. **Normal minimum hemostasis investigations (diagnosis of exclusion).**

Also recommended:

formal registration of BDUC patients (like other mild bleeding disorders) to enable research and consistent care.

Objective Phenotyping : ISTH BAT

- ISTH SSC emphasizes ISTH Bleeding Assessment Tool (BAT) as the foundation for BDUC diagnosis.

TABLE 1 International Society on Thrombosis and Haemostasis Bleeding Assessment Tool bleeding score: normal ranges by age and gender.

Population	Normal range	Cutoff/abnormal BS
Women, 18-30 y	0-4	≥5
Women, 31-51 y	0-5	≥6
Women, 52-88 y	0-6	≥7
Men, 18 y and older	0-3	≥4
Children, <18 y	0-2	≥3

BS, bleeding score derived from the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool [15].

ISTH-BAT

- ISTH-BAT sensitivity for MBD : 75% in general , 100 % in adult women
- Predominance of female cases in BDUC (60-90%)
- High frequency of HMB in BDUC (>60%)
- Higher BS : significant higher risk of future spontaneous bleeding

ISTH-BAT Limitations

- ISTH-BAT sensitivity : lack of sensitivity in those without hemostatic challenges (men & children)
- Score saturation with recurrent symptoms
- Inability of positive BAT to differentiate between different MBD

Laboratory Assessment in the Diagnosis of BDUC

Laboratory Assessment in the Diagnosis of BDUC

- Clinically Exclusion of Ehlers-Dan… …pléments
- Non-hemostatic tests (R/O acquire…
- **First-line hemostasis panel**
- **Second-line / specialized (selected…**
- Additional testing
- BDUC genetic testing

To diagnose BDUC, ISTH SSC recommends

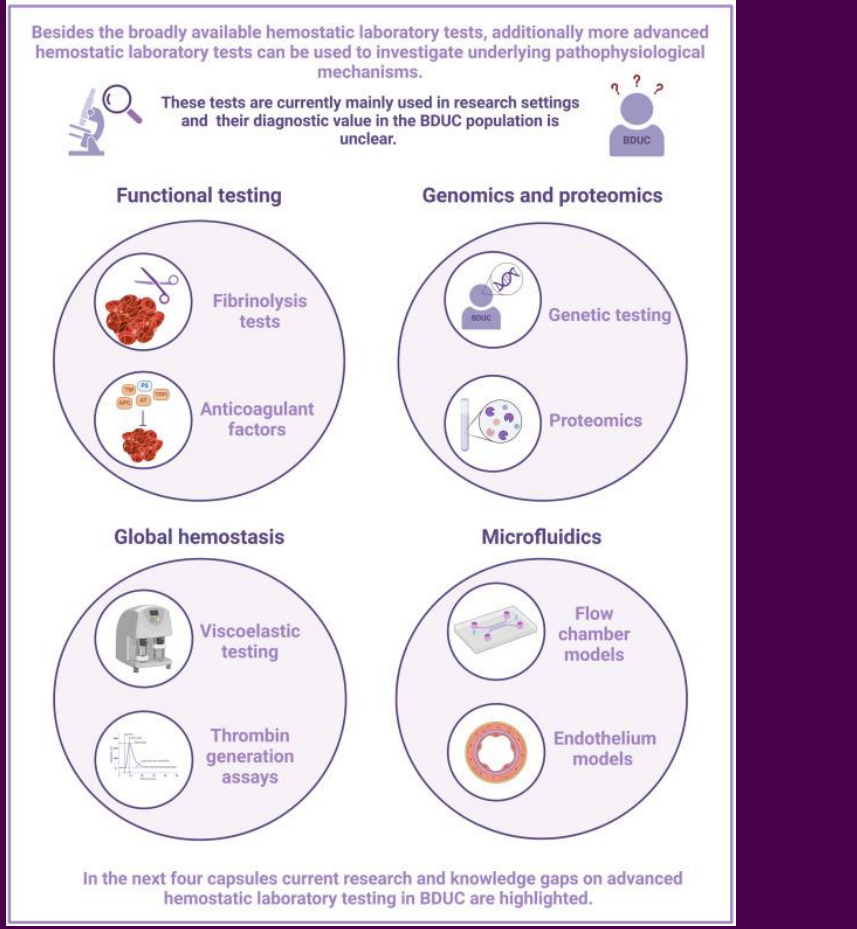
at minimum NORMAL:

- **CBC, PBS**
- **PT, aPTT**
- **Global Hemostatic tests**
- **Fibrinolysis tests**

…ficiencies (incl. FXIII),

- F… Fibrinolysis assays,
- P… Specialized platelet assays,

11. Advanced hemostatic laboratory testing



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Abnormal tests SHOULD be Repeated to Confirm

Specialy for IPFD

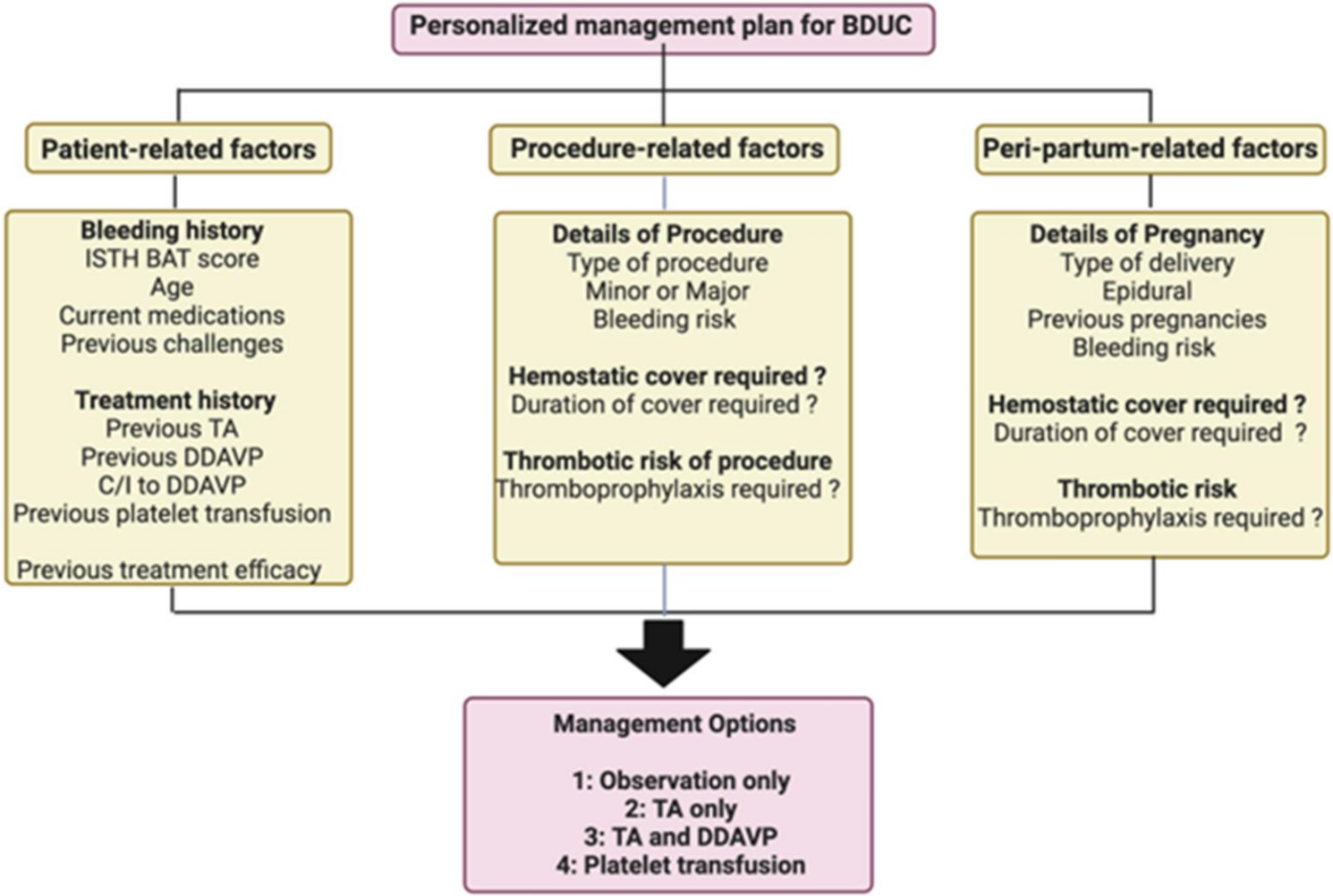
Platelet Testing

LTA remains the gold standard and should be performed at minimum for BDUC diagnosis.

Mild secretion/storage pool defects may be missed by LTA; where possible, consider **dense granule assessment**—but international standardization is still evolving.

PFA-100/200 has **limited** sensitivity for IPFD/VWD and is not recommended as a routine BDUC diagnostic tool.

Referral for Expert Assessment of a Possible Bleeding Tendency


Personalized management plan for BDUC
Patient-related factors
Procedure-related factors
Peri-partum-related factors
Bleeding history
ISTH BAT score
Age
Current medications
Previous challenges
Treatment history
Previous TA
Previous DDAVP
C/I to DDAVP
Previous platelet transfusion
Previous treatment efficacy
Details of Procedure
Type of procedure
Minor or Major
Bleeding risk
Hemostatic cover required ?
Duration of cover required ?
Thrombotic risk of procedure
Thromboprophylaxis required ?
Details of Pregnancy
Type of delivery
Epidural
Previous pregnancies
Bleeding risk
Hemostatic cover required ?
Duration of cover required ?
Thrombotic risk
Thromboprophylaxis required ?
Management Options
1: Observation only
2: TA only
3: TA and DDAVP
4: Platelet transfusion

Peri-Procedural Management

Evidence from retrospective series (≈200 BDUC patients):

- Most received tranexamic acid (TXA) ± desmopressin (DDAVP) (~75.5%).
- Major bleeding: ~5.5% with prophylaxis vs ~30.7% without prophylaxis (retrospective, bias-prone).
- Escalation options (selected cases): platelet transfusion, rFVIIa, plasma—balance against risks (e.g., alloimmunization).

Pregnancy & Childbirth

Evidence limited (retrospective series; 97 deliveries).

- Largest series: without prophylaxis, PPH odds ratio ~6.3; PPH ~78% without prophylaxis vs ~36% with hemostatic agents.
- Practical approach: TXA for most deliveries/procedures; add DDAVP for higher-risk interventions; individualized plan by experienced multidisciplinary team.

Practice Variation

- National survey (Netherlands, 2025): high use of TXA as treatment strategy in BDUC.
- Wiley Online Library PMC2025 dental literature reiterates that ISTH 2024 guidance provides general peri-surgical recommendations; typical options: observation, TXA, TXA+DDAVP, and escalation for invasive surgery.

BDUC at US Hemophilia Treatment Centers

UK

BDUC cases rises sharply since 2012

On 2021 reached to 1061 cases
(2.1 % of bleeding registered patients)

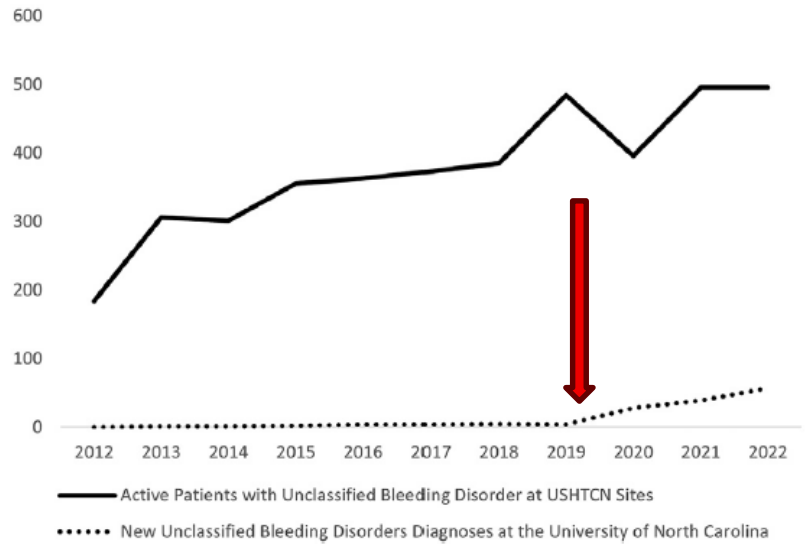


FIGURE Trends in unclassified bleeding disorder diagnosis and registration. Source: Centers for Disease Control and Prevention Community Counts population profile and American Thrombosis and Hemostasis Network dataset. USHTCN, US Hemophilia Treatment Center Network.

In **2023 BDUC** remains a smal but growing segment of bleeding disorder population in **USHTCN**
(2.6% of registered patients in HTC)

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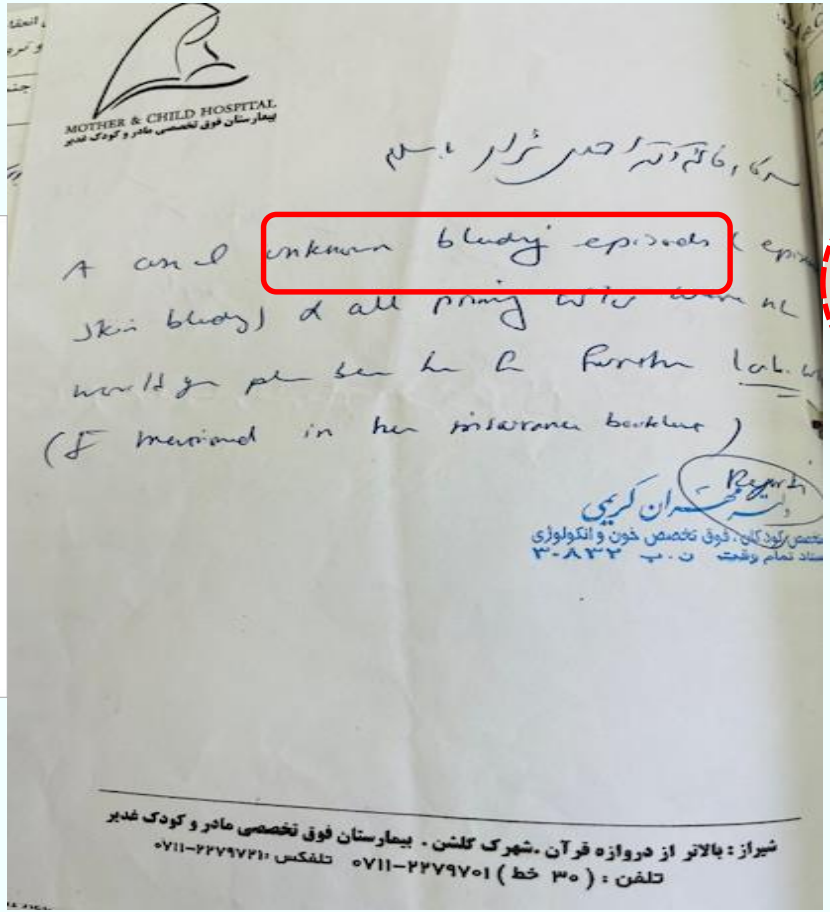
MOTHER & CHILD HOSPITAL
بیمارستان فوق تخصصی مادر و کودک غدیر
A case of unknown bloody episodes
Skin bloody & all
would you please
(if mentioned in her
متخصص کودکان، فوق تخصص خون و انکولوژی
شیراز : بالاتر از دروازه قرآن .شهرک گلشن . بیمارستان فوق تخصصی مادر و کودک غدیر
تلفن : (۳۰ خط) ۰۷۱۱-۲۲۷۹۷۰۱ تلفکس: ۰۷۱۱-۲۲۷۹۷۲۱

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2010

What is Final Diagnosis For the patient
How to manage Dental procedures

Next Step in Iran

- National registration of BDUC patients
- Establishing a national diagnostic & Therapeutic protocol

ممنون از
توجه شما