How I Approach the Patient with Mucocutaneous Bleeding

Peter Kouides, MD
Medical and Research Director,
Mary M. Gooley Hemophilia Center
Clinical Professor of Medicine,
University of Rochester School of Medicine
Rochester, NY
Disclosures

- Possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation:
  - CSL Behring- VWD physician advisory board
  - Baxalta- consultant
  - Octapharma- consultant
  - Grifols- consultant

- No off-label uses to be discussed
Muco-cutaneous bleeding suggestive of defect in primary hemostasis - VWD or PFD

Deep tissue bleeding suggestive of defect in secondary hemostasis - Hemophilia
General Approach: 5 Hints to becoming the best consultant possible—"Kitchenisms"

1. “Think like an internist”

2. “Learn the patterns”

3. “Study how bleeders bleed and clotters clot”

4. “Never discount factitious bleeding/clotting”

5. “Assume you know more than the physician requesting the consult”
More Specific Approach

- Step 1- Collect the specifics of the bleeding symptom… just taking the symptom by report as present is not sufficient
  - Also, usually do not proceed further in the adult if symptom is isolated hematuria or gingival bleeding!

- Step 2- Calculate a bleeding score

- Step 3- If referred bleeding score is relatively low and/or no additional bleeding symptoms besides the referring symptom, strongly consider an anatomic cause
  - Particularly if the bleeding is post-operative, i.e. “Silk deficiency”
Why develop bleeding scores?

- The evaluation of patients presenting with easy bruising or bleeding remains a challenge for the consulting hematologist.

- Mild bleeding events common in patients with and without bleeding disorders.

- What is a “significant bleeding history?” …what constitutes a “bleeder”?

- Increasing interest among researchers and clinicians to more precisely and objectively quantify bleeding symptoms as both research and clinical tools.
In the past decade, many new point of care devices, molecular markers etc. but few bleeding score systems till recently

- FXI deficiency

- Quebec Platelet Disorder
  - McKay H et al, Blood 2004; 104:159-165

- ITP
  - Buchanan GR J Ped 2002; 141:683-688

- VWD- ISTH, EU and Kingston Canada projects
  - Tossetto et al, JTH 2006; 4:766-773
  - Bowman M et al JTH 2010; 8: 213–6
## Poor specificity of bleeding symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% in healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>5-39%</td>
</tr>
<tr>
<td>Gum bleeding</td>
<td>7-51%</td>
</tr>
<tr>
<td>Bruising</td>
<td>12-24%</td>
</tr>
<tr>
<td>Bleeding from trivial wounds</td>
<td>0.2-2%</td>
</tr>
<tr>
<td>Dental extraction related bleeding</td>
<td>1-13%</td>
</tr>
<tr>
<td>Post-tonsillectomy bleeding</td>
<td>2-11%</td>
</tr>
<tr>
<td>Post-partum bleeding</td>
<td>6-23%</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>23-44%</td>
</tr>
</tbody>
</table>

*adapted from Sadler, Blood, 15 MARCH 2003 VOLUME 101, NUMBER 6*
More recent data on the high frequency of bleeding symptoms

- Comprehensive, ontology-backed, web-based questionnaire developed to collect bleeding histories from 500 healthy adults
- Recruitment – online and print ads, primary care waiting rooms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>25%</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>47%</td>
</tr>
<tr>
<td>Blood in stool</td>
<td>19%</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>18%</td>
</tr>
<tr>
<td>Bleeding after tooth extraction</td>
<td>18%</td>
</tr>
</tbody>
</table>

## Discriminatory Power of bleeding symptoms

<table>
<thead>
<tr>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family members with established bleeding disorder</td>
<td>Bruising</td>
<td>Family members with bleeding symptoms</td>
</tr>
<tr>
<td>Profuse bleeding of small wounds</td>
<td>Epistaxis</td>
<td>Gum bleeds</td>
</tr>
<tr>
<td>Profuse surgical-related bleeding esp. T&amp;A, dental</td>
<td>Menorrhagia</td>
<td>Hematuria</td>
</tr>
<tr>
<td>Muscle/joint-related bleeding</td>
<td>Post-partum hemorrhage</td>
<td>BRBPR</td>
</tr>
</tbody>
</table>

Adapted from Sramek et al; Arch Int Med 1995;1409-1415
Improving the significance/specificity of bleeding symptoms

- Summing the symptoms/cumulative score
- Grading the symptom based on degree of intervention
Evolution of the Vicenza score

- **Version 1 (2005):**
  - 0 = none or trivial
  - 1 = present
  - 2 = evaluation by physician
  - 3 = intervention

- **Version 2 (2006), EU scoring system:**
  - -1 = absence of bleeding after hemostatic challenge
  - 4 = blood transfusion or surgery required to control bleeding

The ISTH Bleeding Assessment Score
**Prospective validation of Condensed EU score**

<table>
<thead>
<tr>
<th>Epistaxis</th>
<th>Oral cavity</th>
<th>Surgery</th>
<th>Muscle hematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 No or trivial (less than 5)</td>
<td>0 No</td>
<td>No bleeding in at least 2 surgeries</td>
<td>0 Never</td>
</tr>
<tr>
<td>1 &gt; 5 or more than 10'</td>
<td>1 Reported at least one</td>
<td>Not done or no bleeding in 1 surgery</td>
<td>1 Post-trauma no therapy</td>
</tr>
<tr>
<td>2 CONSULTATION ONLY</td>
<td>2 CONSULTATION ONLY</td>
<td>Reported in &lt;25% of all surgeries</td>
<td>2 Spontaneous no therapy</td>
</tr>
<tr>
<td>3 Packing or Cauterization or Antifibrinolics</td>
<td>3 Surgical hemostasis or Antifibrinolics</td>
<td>Reported in &gt;25% of all surgeries, no intervention</td>
<td>3 Spontaneous or traumatic requiring Desmopressin or Replacement therapy</td>
</tr>
<tr>
<td>4 Blood transfusion or Replacement therapy or Desmopressin</td>
<td>4 Blood transfusion or Replacement therapy or Desmopressin</td>
<td>Surgical hemostasis or Antifibrinolics</td>
<td>4 Spontaneous or traumatic requiring Surgical intervention or Blood transfusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cutaneous</th>
<th>Gi bleeding</th>
<th>Menorrhagia</th>
<th>Hemarthrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 No or trivial (&lt;1 cm)</td>
<td>0 No</td>
<td>No</td>
<td>0 Never</td>
</tr>
<tr>
<td>1 &gt;1 cm and no trauma</td>
<td>1 Associated with ulcer, portal hypertension, hemorrhoids, angiodyssplasia</td>
<td>CONSULTATION ONLY</td>
<td>1 Post-trauma no therapy</td>
</tr>
<tr>
<td>2 CONSULTATION ONLY</td>
<td>2 Spontaneous</td>
<td>Antifibrinolics or pill use</td>
<td>2 Spontaneous no therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Curettage or Iron therapy</td>
<td>3 Spontaneous or traumatic requiring Desmopressin or Replacement therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood transfusion or Replacement therapy or Desmopressin or Antifibrinolics</td>
<td>4 Spontaneous or traumatic requiring Surgical intervention or Blood transfusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding from minor wounds</th>
<th>Tooth extraction</th>
<th>Post-partum hemorrhage</th>
<th>CNS bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 No or trivial (less than 5)</td>
<td>0 No bleeding in at least 2 extractions</td>
<td>No bleeding in at least 2 deliveries</td>
<td>0 Never</td>
</tr>
<tr>
<td>1 &gt; 5 or more than 5'</td>
<td>0 Not done or no bleeding in 1 extraction</td>
<td>Not done or no bleeding in 1 delivery</td>
<td>1 spinal cord bleed</td>
</tr>
<tr>
<td>2 CONSULTATION ONLY</td>
<td>1 Reported in &lt;25% of all procedures</td>
<td>Reported in &gt;25% of all procedures, no intervention</td>
<td>2 Blunt head injury</td>
</tr>
<tr>
<td>3 Surgical hemostasis</td>
<td>2 Reported in &gt;25% of all procedures, no intervention</td>
<td>Surgical hemostasis or Antifibrinolics</td>
<td>3 Subdural, any intervention</td>
</tr>
<tr>
<td>4 Blood transfusion or Replacement therapy or Desmopressin</td>
<td>3 Blood transfusion or Replacement therapy or Desmopressin</td>
<td>Curettage or Iron therapy or Antifibrinolics</td>
<td>4 Intracerebral, any intervention</td>
</tr>
<tr>
<td></td>
<td>4 Resuturing or Packing</td>
<td>Post-partum hemorrhage</td>
<td>Total assigned score:</td>
</tr>
<tr>
<td></td>
<td>4 Blood transfusion or Replacement therapy or Desmopressin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bleeding score issues

- Utility in patients with less challenges/opportunities
  - Children
  - Males

- Applying score to site specific bleeding
  - Heavy menses

- The bleeding score as a predictor of future bleeding
  - Should a patient with borderline reduction in VWF of 42% be treated with desmopressin before tonsillectomy?

- Utility in more severe bleeding and other bleeding disorders
Utility of the Bleeding Score

- **Research Utility**
  - The Vicenza scores and PBQ have the ability to discriminate between healthy subjects and those with VWD.
  - Can be used to describe symptoms and patterns of bleeding in patients with a variety of inherited bleeding disorders.
  - Similarities between scores will improve the quality and standardization of research in this field.

- **Clinical Utility**
  - High negative predictive value → avoid additional lab studies if BS is low.
  - If the bleeding score is high and VWF levels are normal, alternate diagnoses should be actively pursued; semi-empiric hemostatic therapy for invasive procedures.
  - May facilitate communication between caregivers - a “common currency” and establish a more accurate (symptomatic) prevalence of VWD.
Approach to the patient with bruising

**Goal:**
- Distinguish easy bruising from:
  - normal bruising
  - other skin lesions that can be mistaken for bruising
    - AVMs
    - Drug induced purpura
    - Collagen-induced degradation- steroids
    - Drug induced hyperpigmentation mimicking ecchymoses-
      - Hydroxychloroquine, minocycline
    - Vasculitis
  - physical abuse
Specifying bruising

- **Age- “Senile Purpura”: > age 65-**
  - non-palpable, purple bruises with small red patches, which fade to brown over a span of a few weeks
  - often distal forearm, extensor surfaces & legs due to loss of subcutaneous tissue with aging

- **Anorexia/malnutrition- Vit C, Vit K deficiencies**

- **Atraumatic**

- **Distribution: LE, distal UE vs. trunk, face**

- **Frequency: 1-4 x/ mo.**

- **Size: >5 cm diameter or > 5 in toto > 1 cm**

- **Thorough med history of “A>H”?**
  - ASA>β-lactams>Clopidogrel>anti-Depressants>Vit E>Flavinoids>Gingko balboa>other Herbals
Approach to the patient with bruising

Goal:
- Distinguish easy bruising from:
  - normal bruising
  - other skin lesions that can be mistaken for bruising
    » AVMs
    » Drug induced purpura "Think like an internist" - C. Kitchens
    » Collagen-induced degradation- steroids
    » Drug induced hyperpigmentation mimicking ecchymoses-
      • Hydroxychloroquine, minocycline
    » Vasculitis
  - physical abuse "Never discount factitious bleeding" - C. Kitchens
“Learn the patterns”- C. Kitchens-

- Easy bruising + hypermobility
- Determine if they meet Beighton’s criteria for Hypermobility Syndrome (HMS)
<table>
<thead>
<tr>
<th>Specific joint laxity</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive apposition of thumb to forearm</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Passive hyperextension of fingers</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Active hyperextension of elbow &gt; 10 degrees</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Active hyperextension of knee &gt; 10 degrees</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ability to flex spine and place palms to floor without bending knees</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* This score is based upon joint laxity of the above nine anatomic sites. It is calculated by adding all points, with nine being the highest total possible score. A score of four or higher is generally considered an indication of generalized joint laxity.
Specifying Epistaxis

- Duration
  - ? > 10 min

- Frequency
  - ? > > 5 /year

- Severity
  - ? Cautery/packing needed

- Spontaneous
  - ? Unrelated to hypertension, dryness, ASA
    - though curiously level of evidence of each of these risk factors is quite weak
    - Evidence stronger with nasal steroid spray being causative for epistaxis

- Sub-location
  - ? Confined to one nares "Learn the patterns" - C.Kitchens

- Presence of AVMs elsewhere?
Case seen 2 weeks ago- 40 y/o wm for lifelong epistaxis. History is notable for the fact that he is always had epistaxis to the point of requiring cautery and packing in the past but he never recalls being told that they observed an AVM.

Physical exam is notable for the finding of definite AVMs along the hard palate, buccal mucosa and skin of the hands.

Epidemiologic studies suggest likely prevalence rates of HHT between 1:5000 and 1:8000.
Specifying Gum/Dental-related

- Bleeding with flossing
  - ? Unrelated to gingivitis

- Excess bleeding with wisdom teeth removal-
  - ? “dry” socket
  - ? Tea bag needed
  - ? Packing/cautery needed
  - ? Bleeding/oozing > 3 hrs
Specifying Menorrhagia

- Menses perceived as heavy since menarche
- Changes every 30-120 minutes on the heaviest day
- Uses one tampon + one pad or 2 pads/time
- Uses super absorbent brand
- Passes clots size of a quarter
- Frequently stains underclothes
- Loses time from work/school
- History of anemia/Low iron

Tampons/pads with >80 cc blood loss. (Image courtesy of Prof. Rezan Kadir)
The Peril of the Hematologist or Gynecologist evaluating heavy menses without the help of the other!

1. We, hematologists, can miss endometrial cancer as the main cause when referred an older female with heavy menses
2. We, hematologists, can miss anovulatory bleeding as the main cause particularly when referred an adolescent with “heavy” menses
3. The gynecologist may misdiagnose VWD or over-diagnose VWD in women evaluated with “heavy” menses

- **Hematologist, please note**-
  1. Do they have heavy menses in the first place?
  2. Is the menses ovulatory and is the gynecological exam normal?

- **Gynecologist, please note**-
  1. Is the patient blood group O and just happen to have borderline low VWF levels?
  2. Was testing done long distance through a national lab?
History taking in the patient with “heavy” menses, Part I

Gynecological

• Menstrual pattern of ovulation
  » Are periods regular within a 21 days- 37 days?

Historically VWD prevalence studies in HMB required ovulatory pattern and normal gyn exam

» Do they have any of the Warner criteria-clinical features that are associated most strongly with increased menstrual blood loss volume:

  i. required rate of changing sanitary protection during full flow (< 1-2 hrs)
  ii. poor iron status (subnormal ferritin)
  iii. size of clots (> quarter)
  iv. total number of products used
  v. need to change protection during the night

76% prediction success for MBL > 80 ml if criteria i-iii

» Pictorial Chart Score assessment

» Results of pelvic exam from gynecologist

When the case is not “clean”

- i.e. concurrent gynecological abnormality?
  - Dutch single-center prospective cohort study of 112 consecutive patients referred for HMB.
  - Control subjects 28 healthy volunteers who reported no HMB.
  - Hemostatic testing in the first week after menstruation
  - Patients underwent gynecologic evaluation.
  - Median age 42.5 years (range, 17-55 years) in patients and 40.0 years (range, 25-55 years) in control subjects. 46% of patients had anemia;
  - median pictorial bleeding assessment chart score was 271

26% of patients had gynecologic abnormalities, which was felt to explain HMB!
  - 9% uterine polyps and 17% submucous uterine fibroid tumors

Bleeding disorders in explained and unexplained heavy menstrual bleeding

<table>
<thead>
<tr>
<th>Variables, n (%)</th>
<th>Unexplained (n = 76)</th>
<th>Explained (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding disorder overall</td>
<td>23 (31)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Platelet defect</td>
<td>16 (21)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Coagulation factor deficiencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Von Willebrand's disease</td>
<td>5 (7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Low factor XI (&lt;70%)</td>
<td>3 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Factor VII deficiency</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Combination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet defect and Von Willebrand's disease</td>
<td>1 (1)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Platelet defect and low factor XI</td>
<td>1 (1)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

History taking in the menorrhagic patient, Part II

- PMH for conditions associated with bleeding:
  - Chronic liver disease
  - Renal Disease
  - Cushing Syndrome
  - Thyroid disease, particularly hypothyroidism
    » Stuijver et al-Haemophilia (2014), 20, 326–332
      • In patients with newly diagnosed hypothyroidism-
        » 9/30 (30%) with aVWD had HMB c/w 9/61 (15%)

- Family History

"Think like an internist" - C. Kitchens
Specifying Post-partum Hemorrhage

- Must also consider the 3 T’s…Tone, Tissue and Trauma

<table>
<thead>
<tr>
<th>1. Uterine atony</th>
<th>3. Uterine/cervical/vaginal trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Induction of labor</td>
<td>a) Instrumental delivery</td>
</tr>
<tr>
<td>b) Labor &gt;12 hours</td>
<td>b) C/S</td>
</tr>
<tr>
<td>c) Prolonged third stage</td>
<td></td>
</tr>
<tr>
<td>d) Multiple pregnancies</td>
<td></td>
</tr>
<tr>
<td>e) Maternal obesity</td>
<td></td>
</tr>
<tr>
<td>f) Baby &gt;4 kg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Placental abnormalities</th>
<th>4. Hemostatic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Retained placenta</td>
<td>a) Acquired</td>
</tr>
<tr>
<td>b) Placenta previa</td>
<td>i. Anticoagulant therapy</td>
</tr>
<tr>
<td>c) Placenta abruption</td>
<td>ii. Uremia, liver disease</td>
</tr>
<tr>
<td></td>
<td>iii. DIC: maternal sepsis, amniotic</td>
</tr>
<tr>
<td></td>
<td>fluid embolism, placental abruption, massive transfusion</td>
</tr>
</tbody>
</table>

```
“Think like an internist”- C. Kitchens
..Think like a gynecologist
```
What to do when bleeding history is not confirmed by laboratory testing?

- Quiroga et al.
- n=280 patients/299 controls referred with mucocutaneous bleeding

### Distribution of Dx

- 60% VWD
- 23% PFD
- 17% Mild Coag
- 12% Combined
- 3% Unknown

### Reasons for normal hemostasis evaluation:

1. Components of standard VWD panel are subject to acute changes as “acute phase reactants.”
2. Severity of bleeding manifestations often does not correspond to the level of VWF measured by present diagnostic assays.
3. Present diagnostic testing does not account for the the high shear-rate conditions in vivo where the effect of low VWF is manifest when bleeding occurs.
4. Present measures of platelet function and hyperfibrinolysis not very sensitive
Patient E.A.- Should the bleeding score trump the lab results in terms of management?

37 y/o scheduled for rhinoplasty. You are asked to give recommendations for prophylaxis of bleeding given following muco-cutaneous bleeding history (EU Bleeding score (BS) 12 pts)-

- Severe postpartum hemorrhage with the last two of her four pregnancies having bled down; after her 3rd pregnancy in 2001 she bled to a HCT of 11% needing three units and then in 2003 she bled again and had emergent D&C. We don’t know if she had retained products of conception. (EU BS 3 pts)
- Extensive bleeding after dental extraction two years ago requiring an ED visit for packing. (EU BS 3 pts)
- Excessive bleeding after a laparoscopic cholecystectomy in 1992 when what was expected to be less than 2 hour procedure required eight hours of operation because of bleeding (EU BS 3 pts)
- Easy bruising (EU BS 1 pt)
- Periodic epistaxis 3-4/yr > 10 min (EU BS 1 pt).
- Chronic menorrhagia for the last 4-5 years where she is changing every 1-2 hours on her heaviest day going through at least a pack of pads each time. (EU BS 1 pt)
Exhaustive hemostasis work up negative

<table>
<thead>
<tr>
<th>HCT</th>
<th>PLT</th>
<th>I.N.R.</th>
<th>APTT</th>
<th>VWF AG</th>
<th>RiCof</th>
<th>FACTOR VIII</th>
<th>CLOSURE TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>251</td>
<td>1.1</td>
<td>28.0</td>
<td>99</td>
<td>94</td>
<td>106</td>
<td>109</td>
</tr>
</tbody>
</table>

- Platelet aggregation and release with WB- WNL
- Fibrinogen 320 mg/dl; FIX 84% ; FXI-120% ; FXIII-normal
- ECL: >2 hours, TT: 18.2 (WNL)
- PAI, anti-plasmin WNL

Are there any additional tests to order?

Off label, is there a role for TEG or thrombin generation assays?

Would you advise any prophylactic therapy to reduce perceived marked increased bleeding risk?
A semi-empiric approach to UBD (unclassified bleeding disorder)

Summary

• Not all bleeding is from an underlying disorder of hemostasis!
• Be suspicious that there is not an underlying bleeding disorder if the symptom is isolated!
  • "Assume you know more than the physician requesting the consult" - C. Kitchens
• Bleeding score is not perfect but excellent negative predictive value
• If positive with normal hemostasis evaluation, i.e. “UBD”, then semi-empiric therapy may be in order