Females with Bleeding Disorders: Ongoing initiatives and research.

Robert F. Sidonio, Jr. MD, MSc.
Associate Clinical Director of Hemostasis and Thrombosis
State Hemophilia Meeting
HTRS MRA and HOG Clinical Scientist
March 2, 2017
Disclosures

- ATHN VWD
  - Funded by Baxalta

- Investigator initiated studies
  - Grifols
  - Bioverativ

- HTRS MRA grant
  - Funded by Baxalta

- Advisory Boards and Trial Steering Cmtes
  - Baxalta, Pfizer, Emergent Solutions, Octapharma, Grifols, Biogen and CSL Behring, Novo Nordisk
Objectives

• Scope of the problem

• Prevalence of Heavy Menstrual Bleeding (HMB)

• Strategies in HMB management

• Ongoing initiatives
Case

• 14 YOWF presents to ED for heavy periods

• She reports she feels dizzy and unable to attend school this week and mother feels she is more pale

• PMH
  – No chronic medical problems
  – NKDA

• PSH
  – Prolonged oozing with dental extraction
  – No other surgeries or skin biopsies
Case

• What additional questions should be asked?
Phillip Screening Tool

- Adapted for ED use
  - On average does your period last 7 or more days?
  - Do you experience “flooding” or overflow bleeding through your pad?
  - Do you need to change your pad more than every 1-2 hours at times during your cycle?
  - Have you ever been treated for iron deficiency anemia?
  - Do you have a family history of a bleeding disorder?
  - Have you had excessive bleeding with dental extraction or surgery?
  - Have you ever had excessive bleeding with a miscarriage or following delivery of a child?
Phillip Screening Tool

How well does it work?

• Sensitivity of 82%
• Specificity of 24%

If PBAC >185
• Sensitivity 95%
• Specificity 16%

Higham JM et al.  BJOG 1990
Siboni SM et al.  Haemophilia 2009
Heavy menstrual bleeding

- > 7 days of menstrual bleeding
- > 80mL of blood per menstrual cycle

**Predictive of heavy menstrual bleeding**
- Clots >1 inch (grape size)
- Iron deficiency anemia
- Changing a pad/tampon every hour at times
PBAC

- If prospectively evaluated:
  - Record for 3 months and average

- Flooding
  - Any time during period 5 points

- Clots (Importance to record)
  - ½ inch clots 1 point
  - 1 inch clots 5 points
Case:
Pictorial Bleeding Assessment Chart

- **PBAC score**
  - \((6 \times 5) + (20 \times 20)\)
  - 430
  - \(\geq 100\) correlates with ~80cc/cycle
    - 86% sens. and 89% spec.
  - \(\geq 185\) able to discriminate between VWD and normals

Higham et al. BJH 1990
Siboni HM et al. Haemophilia 2009
Revel-Vilk S et al. Jpeds 2012
SISTERHOOD
A NEW APP FOR WOMEN WITH BLEEDING DISORDERS!

- Track Monthly Menstrual Cycle
- Log Symptoms
- Record Type Of Treatment Used
- Period Reminder Alert
- Log Notes For Healthcare Provider
- Easily Share Information With Your Provider

Download for FREE!

Hemophilia Federation of America | hemophiliaafed.org

Available on the App Store | Android App On Google Play
Menstrual diary app

Monthly Tracking

<table>
<thead>
<tr>
<th>Month</th>
<th>Days Bled</th>
<th>Days</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 2014</td>
<td>0</td>
<td>28</td>
<td>0%</td>
</tr>
<tr>
<td>March 2014</td>
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<td>31</td>
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<tr>
<td>April 2014</td>
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<td>May 2014</td>
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<tr>
<td>June 2014</td>
<td>10</td>
<td>30</td>
<td>33%</td>
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<tr>
<td>July 2014</td>
<td>12</td>
<td>31</td>
<td>39%</td>
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<tr>
<td>August 2014</td>
<td>9</td>
<td>31</td>
<td>29%</td>
</tr>
<tr>
<td>September 2014</td>
<td>11</td>
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<td>37%</td>
</tr>
<tr>
<td>October 2014</td>
<td>11</td>
<td>31</td>
<td>35%</td>
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<tr>
<td>November 2014</td>
<td>10</td>
<td>30</td>
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</tr>
<tr>
<td>December 2014</td>
<td>9</td>
<td>31</td>
<td>29%</td>
</tr>
<tr>
<td>January 2015</td>
<td>10</td>
<td>31</td>
<td>32%</td>
</tr>
</tbody>
</table>

Updates coming early March 2017
Updates

- Reminder to log menstrual bleeding
- Easier ability to email menstrual diary to provider
- Alerts if menstrual bleeding is very heavy
Case

• How do you decide what level (if any) of hemostatic investigation is warranted?
Established guideline in need of validation

Lab evaluation in setting of abnormal uterine bleeding

- CBC
- PT, aPTT, Fibrinogen activity
- VWD panel (FVIII:C, VWF:Ag, VWF:RCo)
- Hypothyroidism evaluation
- +/- Pregnancy test
Case

- What are the most common reasons for heavy menstrual bleeding in adolescents?
# Causes of Heavy Menstrual Bleeding by Age

<table>
<thead>
<tr>
<th>Cause</th>
<th>Age 13-19</th>
<th>Age 20-34</th>
<th>Age 35-49</th>
<th>Age 50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent anovulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New systemic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-op complication</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peri-menopausal anovulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Courtesy Andra James and FWGBD
Anovulatory bleeding

- Without ovulation, there is no corpus luteum to secrete progesterone, ovarian estrogen is then unopposed, maintaining the endometrium in the proliferative phase.

- This causes endometrial thickening and irregular, often heavy, menses due to incomplete shedding of the unstable endometrium.
# Heavy menstrual bleeding

How common are bleeding disorders when presenting with heavy menstrual bleeding?

<table>
<thead>
<tr>
<th>Bleeding Disorder</th>
<th>Prevalence in women and teenage girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Willebrand disease</td>
<td>10% (4-36%)</td>
</tr>
<tr>
<td>Platelet dysfunction</td>
<td>20% (2-44%)</td>
</tr>
<tr>
<td>FXI deficiency</td>
<td>1-2%</td>
</tr>
<tr>
<td>Low FVIII (factor 8)</td>
<td>8%</td>
</tr>
<tr>
<td>Low platelets</td>
<td>5%</td>
</tr>
<tr>
<td>Rare factor deficiencies</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Dilley A et al. Obstet Gynecol 2001  
Krause M et al. Thromb and Haemost 2001  
Kadir RA. Semin Hemtol 1999
Case

• What is the best approach to management of heavy menstrual bleeding in adolescents with and without an identified bleeding disorder?
Menstrual bleeding reduction options

• Hormonal therapies
  – Estrogens
    • Patch
    • Ring
    • Pills/IV
  – Combined oral contraceptives
  – Progestins
    • Oral progestins (Aygestin)
    • Depo Provera (IM)
    • Progestin implants
  – Intrauterine device
  – GnRH analogues
Common approaches

• **Aygestin (Norethindrone) 5-10mg daily**
  – Progestin only pill (POP)
  – Useful if thrombosis risk factors
  – For adolescent girls <50kg consider 5mg daily first
  – Anticipate control with complete secondary amenorrhea in 4-8 weeks
  – No sugar or placebo pills
  – Common SE: Emotional lability, fatigue
  – Least effective form of oral birth control
  – At least 10 patients with bleeding disorders and no periods for >12 months
Common approaches

• **Combined oral contraceptives (COC)**
  
  – Combines a progestin and estrogen
  – CI if HTN, migraine HA with aura, thrombosis, PE or stroke
  – Good for general use
  – Best options are:
    • Levora, Lo-oigestrel, Loestrin
  – Consider COC with anti-androgenic progestins if acne is an issue
    • Norgestimate or drospirenone
      – Examples include Ocella, Yasmin, Ortho tricyclen
  – Works well for obese patients, control irregular bleeding and those with ovarian cysts, PCOS or dysmenorrhea
  – Common strategy
    • COC taper with 1 tab Q6h x 4 d then Q8h x 3d then Q12h x 2d then daily
    • Often will skip placebo pills 2 months then have withdrawal bleed every 3 months
Strategies addressing HMB in adolescents

• Creation of combined women’s bleeding disorder clinic
  – Multi-disciplinary clinic once a month at Emory University Gyn clinic and once a month at Egleston

• Create clinical pathway for adolescent girls with heavy menstrual bleeding
  – Unified diagnostic and management algorithm

• Clinical trials and studies
  – EHF products in hemophilia carriers
  – DDAVP in Carriers
  – ATHENA study (ATHN Dream award)
Multidisciplinary clinic

Developing a multidisciplinary Young Women’s Blood Disorders Program: a single-centre approach with guidance for other centres

A. ZIA,*†‡ M. LAU,*† J. JOURNEYCAKE,*†‡ R. SARODE,§ J. MARSHALL,‡
N. DE SIMONE,§ E. WILSON,¶ A. WINBORN‡ and P. KOUIDES**
Role of the HTC for women with bleeding disorders

- Support development and implementation of women’s programs
- Educate primary care providers about women with bleeding disorders
- Efficiently utilize medical resources
- Provide prenatal care visit
  • Pregnancy and delivery plan
- Coordinate surgeries
- Co-manage heavy menstrual bleeding

Winikoff, et al. Haemophilia 2004
Combined Women’s Bleeding Disorder Clinic

• Over the last 9 months at Emory University

• 35 adolescent females seen (multiple visits)
  – 10 with VWD
  – 2 hemophilia carriers
  – 4 with qualitative platelet function
  – 13 with PCOS or anovulatory bleeding
  – 5 with hypercoaguable state
  – 1 with ITP

• Treatments utilized
  – COC (n=16)
  – Aygestin (n=14)
  – IUD (n=2)
  – Depo Provera (n=2)
CHOA Adolescent Girls clinic

- Over the last 12 months Kelly and I have seen 77 adolescent girls with primary CC of HMB
  - Additionally 169 seen by other providers

- ½ day (Wed. afternoon) once a month

- Packet created
  - Menstrual Bleeding questionnaire
  - Promis 25
  - Menorrhagia Impact Questionnaire
  - Pictorial Bleeding Assessment chart
Strategies addressing HMB in adolescents

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Strategies addressing HMB in adolescents

Screening Questions (Adapted from Claire Phillip Screening tool; AMQG 2011)
1. On average does your period last 7 or more days?
2. Do you experience "flooding" or overflow bleeding through your tampon or pad?
3. Do you need to change your pad or tampon more than every 1-2 hours at times during your period?
4. Have you ever been treated (iron pills, blood transfusion, etc.) for iron deficiency anemia in the past?
5. Do you have a family history of a bleeding disorder?
6. Have you had excessive bleeding with a dental extraction or dental surgery?
7. Have you had excessive bleeding with a miscarriage or following delivery of a child?

Considered to be positive if answered yes to any of the above questions

Algorithm

General Care
- Monitor vitals per routine
- Orthostatic blood pressure x1
- Start IV if indicated

1. Symptoms of Anemia
   - Tachycardia
   - Orthostatic
   - Headache/Dizziness
   - Acute fatigue

2. Admission Criteria
   - Hgb < 9
   - Symptomatic of anemia
   - Tachycardia/ hypotension, consider PICU transfer

First Line Hormone Therapy (See Table 3)

Heavy Menstrual Bleeding Clinical Practice Guideline

Inpatient Management
Inclusion Criteria: Menstruating females with concern for heavy bleeding
Exclusion Criteria: Previously identified bleeding disorder

Algorithm

Patient admitted with Heavy Menstrual Bleeding
If admitted from ED, continue from previous treatment

Screening Questions (See Table 1)

1. Symptoms of Anemia
   - Tachycardia
   - Orthostatic
   - Headache/Dizziness
   - Acute fatigue

2. Transfusion
   - Consider transfusing with 1-2 units of PRBCs if
     - Hgb < 7 and patient orthostatic
     - Hgb < 6

General Care
- Monitor vitals per routine
- Obtain orthostatic blood pressure
- Simultaneous bleeding
- Start IV if indicated

3. Discharge Criteria
   - Tolerating PO
   - No bleeding
   - No longer orthostatic

4. Discharge Instructions
   - Follow-up with Gynecologist in
   - Emory Family Planning/Gynecology Clinic (404.778.3401)
   - Hughes Spalding Adolescent Medicine Clinic (404.778.9595)
   - in 1-2 weeks
   - Follow-up with the Hematology Clinic (404.778.1319)
   - in 4-6 weeks to complete bleeding disorder workup
   - Iron suppletion if indicated and encourage iron rich foods

5. Discharge Criteria
   - No
   - Discharge home

6. Discharge Instructions
   - If no improvement after loading dose and 4 doses of Amicar, consider:
     - 1-2 units PRBCs (if Hgb < 9)
     - Stop Premarin
     - Start Le-Dural QSH
     - Consult Gynecology
   - Bleeding stopped?
   - No
   - Discharge home
   - Discharge home

7. Discharge Instructions
   - If no improvement after loading dose and 4 doses of Amicar, consider:
     - 1-2 units PRBCs (if Hgb < 9)
     - Stop Premarin
     - Start Le-Dural QSH
     - Consult Gynecology
   - Bleeding stopped?
   - No
   - Discharge home

Developed through the efforts of Children’s Healthcare of Atlanta and physicians on Children’s medical staff in the translation of advancing pediatric healthcare. This is a general guide and does not represent a professional care standard agreement between providers' obligation to patients. Ultimately the patient’s physician must determine the most appropriate care. © 2015 Children’s Healthcare of Atlanta, Inc.
Case

- 14 YOWF presents to ED for HMB with a PBAC of 430
  - Reports changing pads every 1-2 hours at times
  - Period often lasts more than 7 days
  - Misses school because of flooding and difficulty changing pads during class
  - Oozing with dental procedures

Screening Questions (Adapted from Claire Phillip Screening tool; AMJOG 2011)

1. On average does your period last 7 or more days?
2. Do you experience “flooding” or overflow bleeding through your tampon or pad?
3. Do you need to change your pad or tampon more than every 1-2 hours at times during your period?
4. Have you ever been treated (iron pills, blood transfusion, etc.) for iron deficiency anemia in the past?
5. Do you have a family history of a bleeding disorder?
6. Have you had excessive bleeding with a dental extraction or dental surgery?
7. Have you had excessive bleeding with a miscarriage or following delivery of a child?

*Considered to be positive if answered yes to any of the above questions*
Heavy menstrual bleeding orderset

**Clinical Practice Guideline for ED Heavy Menstrual Bleeding**

**Order Sets**
- **Initiate Guideline**
  - Exclude Patient in ED HMB Guideline
  - Include Patient in ED HMB Guideline
  - Routine + ONGOING starting Today at 10:15 until Specified

**Nursing**
- **Vital Signs**
  - Vital Signs with Orthostatic Pulse and BP
  - Insert and Maintain IV

**Consults**
- **Consults**
  - Hematology/Oncology Consult
  - Gynecology Consult

**Lab**
- **CBC**
  - Stat, Once, Ongoing with HGB
- **Pregnancy Serum Qual**
  - Stat, Once
- **PT/PTT Panel**
  - Stat, Once
- **Thromboelastograph**
  - Stat, Once
- **Fibrinogen Activity**
  - Stat, Once
- **Inova + TIBC**
  - Stat, Once
- **TSH with Reflex T4 Free**
  - Stat, Once
- **Von Willebrand Profile**
  - Stat, Once
- **Type and Screen**
  - Stat, Once
- **GGT/Transaminases by Amplification**
  - Stat, Once

**Radiology**
- **US Pelvis Non OB**
  - Stat, Imaging Once

**Heavy Menstrual Bleeding Medications**
- **Hormone Therapy**
  - Conjugated Estrogens (PREMARIN) injection 25 mg, SQ, X1
  - NON-FORM **norethindrone Acetate tab** 5 mg, Oral, X1
  - medroxyPROGESTERONE (PROGESTRA) 10 mg, Oral, X1

- **Other Medications**
  - levoBESIDE (LEFIVAN) injection solution 1,000 mg, IV, X1
  - oralmin (ZOFRAN) injection solution 5 mg, IV, X1
  - Ferrous Sulfate (55 mg elemental iron) 1 tab, Oral, X1
  - Dicoumarol (COFLAC) capsules 100, 100 mg, Oral, X1
Screening smartphrase

Heavy Menstrual Bleeding Screening Questions

1. On average does your period last 7 or more days? {YES/NO:220027}
2. Do you experience “flooding” or overflow bleeding through your tampon or pad? {YES/NO:220027}
3. Do you need to change your pad or tampon more than every 1-2 hours at times during your period? {YES/NO:220027}
4. Have you ever been treated (iron pills, blood transfusions, etc.) for iron deficiency anemia in the past? {YES/NO:220027}
5. Do you have a family history of a bleeding disorder? {YES/NO:220027}
6. Have you had excessive bleeding with a dental extraction or dental surgery? {YES/NO:220027}
7. Have you had excessive bleeding with a miscarriage or following delivery of a child? {YES/NO:220027}

**Considered to be positive if answered yes to any of the above questions**
Menstrual bleeding assessment

<table>
<thead>
<tr>
<th>Human Milk Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Output</td>
</tr>
<tr>
<td>Elimination Status</td>
</tr>
<tr>
<td>Urine (mL)</td>
</tr>
<tr>
<td>Urinary Frequency</td>
</tr>
<tr>
<td>Emesis (mL)</td>
</tr>
<tr>
<td>Emesis Frequency</td>
</tr>
<tr>
<td>Stool (mL)</td>
</tr>
<tr>
<td>Stool Frequency</td>
</tr>
<tr>
<td>Menstrual Blood Loss Frequency</td>
</tr>
<tr>
<td>Menstrual Blood Loss Description</td>
</tr>
</tbody>
</table>

The frequency is the number of sanitary items used in that hour. Description is from a pick list. You only see these rows when the patient is a female greater than 10 years.
ED management

Screening Questions
Consult Hematology if known history of blood thinners or ICP

Positive Screening?

No

Patient Actively Bleeding?

No

Yes

Labs
(See Table 1)

Yes
ED management

- Patient Actively Bleeding?
  - No → CBC and Serum Pregnancy Test
  - WNL and Negative?
    - No → Consider other causes
    - Yes → Discharge for outpatient follow-up
  - Yes → No discharge hormone needed
ED management

Box 1: Labs

Obtain: CBC and Serum Pregnancy

If screening positive, obtain the following labs: PT, aPTT, Fibrinogen Activity, Thrombin time, TSH with reflex to free T4, Type and Screen, TIBC & Ferritin, VonWillebrand Profile: (Factor 8, VW antigen, Ristocetin cofactor)

Consider: Ultrasound (Pelvis Non OB): if pain or concern for mass
Urine GC/Chlamydia: if concern for STI (Consider RPR and HIV)

Labs Resulting in Real Time (< 1 hr): PT, aPTT, and Fibrinogen Activity
If abnormal, consult Hem/Onc: PT ≥ 17 seconds | aPTT ≥ 40 seconds | Fib < 150

Labs to be Followed by Hem/Onc:
Thrombin time, TSH with reflex to free T4, Type and Screen, TIBC & Ferritin, VonWillebrand Profile: (Factor 8, VW antigen, Ristocetin cofactor)

Abnormal labs resulting after discharge will be received by Transfer Center who will contact the Clinical Director of Hemostasis/Thrombosis
ED management

If already taking an oral combined oral contraceptive (COC), discontinue and begin the following therapy.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Max Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line Hormone Therapy</strong></td>
<td><img src="https://via.placeholder.com/150" alt="Diagram" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjugated Estrogens (Premarin)</td>
<td>25 mg IV x1, If bleeding continues consider repeating after 4 hours</td>
<td>25 mg/dose</td>
<td>Contraindicated if history of DVT or Pulmonary Emboli, Lupus, Kawasaki’s Disease, Nephrotic Syndrome, and/or, Congenital Cardiac Condition warranting daily Aspirin or Anticoagulant such as single ventricle physiology</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>5 mg PO x1, If bleeding continues consider repeating after 4 hours</td>
<td>5 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>10 mg PO x1</td>
<td>10 mg/dose</td>
<td>If Conjugated Premarin or Norethindrone contraindicated</td>
</tr>
</tbody>
</table>
ED management

Mild or No Anemia
Hgb >9

Symptomatic Anemia? ✔

Discharge for outpatient follow-up with hormone taper

Moderate Anemia
Hgb 8 to ≤9

First Line Hormone Therapy
(See Table 2)

Severe Anemia
Hgb <8

First Line Hormone Therapy
(See Table 2)

Consider
- Ultrasound (Pelvis Non OB)
- Consider 1 unit PRBCs
  If Hgb <7 and patient orthostatic or Hgb <6
- Urine GC/Chlamydia

Admit to Hospital
### Table 1: ED Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Max Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line Hormone Therapy</strong></td>
<td></td>
<td></td>
<td><strong>If already taking an oral combined oral contraceptive (COC), discontinue and begin the following therapy.</strong></td>
</tr>
<tr>
<td>Conjugated Estrogens (Premarin) Preferred</td>
<td>25 mg IV x1, If bleeding continues consider repeating after 4 hours</td>
<td>25 mg/dose</td>
<td>Contraindicated if history of DVT or Pulmonary Emboli, Lupus, Kawasaki's Disease, Nephrotic Syndrome, and/or, Congenital Cardiac Condition warranting daily Aspirin or Anticoagulant such as single ventricle physiology</td>
</tr>
<tr>
<td>Norethindrone Alternative</td>
<td>5 mg PO x1, If bleeding continues consider repeating after 4 hours</td>
<td>5 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone Alternative</td>
<td>10 mg PO x1</td>
<td>10 mg/dose</td>
<td>If Conjugated Premarin or Norethindrone contraindicated</td>
</tr>
<tr>
<td><strong>Supplemental Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous Sulfate</td>
<td>325 mg (65 mg elemental iron) PO x1</td>
<td>325 mg/dose</td>
<td>If Hgb &lt;10, start if tolerating PO</td>
</tr>
<tr>
<td>Docusate (Colace)</td>
<td>50-100 mg x1</td>
<td>100 mg/dose</td>
<td>If iron given</td>
</tr>
<tr>
<td>Ondansetron (Zofran)</td>
<td>0.15/mg/kg PO or IV x1</td>
<td>8 mg/dose</td>
<td>If IV or oral hormone therapy given</td>
</tr>
<tr>
<td>Ranitidine (Zantac)</td>
<td>1 mg/kg IV x1</td>
<td>50 mg/dose</td>
<td>If IV or oral hormone therapy given</td>
</tr>
</tbody>
</table>

### Table 2: Discharge Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Max Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discharge Hormone Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lo-Ovral (Preferred)</td>
<td>1 tab PO Q8 x 3 days, then 1 tab PO Q12 x 2 days, then 1 tab PO QD</td>
<td>1 tab/dose</td>
<td>If bleeding recurs, return to prior dose and call doctor; Alternative Loestrin/Levora</td>
</tr>
<tr>
<td>Norethindrone (Alternative)</td>
<td>5 mg PO Q6 until bleeding stops, then 5 mg PO Q8 x 4 days, then 5 mg PO Q12 x 1 week, then 5 mg QD</td>
<td>5 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone (Alternative)</td>
<td>10 mg PO Q6 x 4 days, then 10 mg PO Q8 x 3 days, then 10 mg PO Q12 x 2 days, then 10 mg PO QD</td>
<td>10 mg/dose</td>
<td>If Lo-Ovral or Norethindrone contraindicated</td>
</tr>
<tr>
<td><strong>Supplemental Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous Sulfate</td>
<td>325 mg (65 mg elemental iron) PO Q12</td>
<td>325 mg/dose</td>
<td>If Hgb &lt;10, start if tolerating PO</td>
</tr>
<tr>
<td>Ondansetron (Zofran)</td>
<td>0.15 mg/kg PO Q8</td>
<td>8 mg/dose</td>
<td>If oral hormone therapy given</td>
</tr>
<tr>
<td>Ranitidine (Zantac)</td>
<td>2 mg/kg PO QD</td>
<td>150 mg/dose</td>
<td>If oral hormone therapy given</td>
</tr>
<tr>
<td>Docusate (Colace)</td>
<td>50-100 mg QD</td>
<td>100 mg/dose</td>
<td>If iron given</td>
</tr>
</tbody>
</table>
Inpatient management

Mild or No Anemia
Hgb >9

Symptomatic Anemia? Yes

First Line Hormone Therapy
(See Table 3)

Bleeding Persists for >24 hours on Conjugated Premarin IV?

Yes

- Start Amicar or Tranexamic Acid
- Continue Premarin
- Consult Hematology
- Consider Ultrasound (Pelvis Non OB)

Oral Hormone Taper
(See Table 3)

Oral Hormone Taper
(See Table 3)

Meets Discharge Criteria?

Yes

Discharge home

No

Discharge home

Severe Anemia
Hgb <8
Consider transfusion

Moderate Anemia
Hgb 8 to ≤9

No

No

If no improvement after loading dose and 4 doses of Amicar, consider:

- 1-2 units PRBCs (if Hgb <9)
- Stop Premarin
- Start Lo-Ovral Q6H
- Consult Gynecology
# Inpatient Medications

## Table 1: Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Max Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line Hormone Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjugated Estrogens (Premarin)</td>
<td>25 mg IV Q4H until bleeding stops</td>
<td>25 mg/dose</td>
<td>Contraindicated if history of DVT or Pulmonary Emboli, Lupus, Kawasaki’s Disease, Nephrotic Syndrome, and/or, congenital cardiac condition that warrants daily Aspirin or anticoagulant such as single ventricle physiology</td>
</tr>
<tr>
<td>Preferred</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norethindrone</td>
<td>5 mg PO Q4H until bleeding stops</td>
<td>5 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Alternative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>10 mg PO Q6H</td>
<td>10 mg/dose</td>
<td>If Conjugated Premarin, Norethindrone, or Lo-Ovral contraindicated</td>
</tr>
<tr>
<td>Alternative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance and Discharge Hormone Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lo-Ovral</td>
<td>1 tab PO Q6H x 4 days then 1 tab PO Q8H x 3 days, then 1 tab PO Q12H x 2 days, then 1 tab PO QD</td>
<td>1 tab/dose</td>
<td>If bleeding recurs, return to prior dose; Alternative Loestrin/Levora; Contraindicated if history of DVT or Pulmonary Emboli, Lupus, Kawasaki’s Disease, Nephrotic Syndrome, and/or, congenital cardiac condition that warrants daily Aspirin or anticoagulant such as single, ventricle physiology</td>
</tr>
<tr>
<td>Preferred</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norethindrone</td>
<td>5 mg PO Q6H x 4 days, then 5 mg PO Q8H x 4 days, then 5 mg PO Q12H x 1 week, then 5 mg PO QD</td>
<td>5 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Alternative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>10 mg tab PO Q6 x 4 days, then 10 mg tab PO Q8 x 3 days, then 10 mg tab PO Q12H x 2 days, then 10 mg tab PO QD</td>
<td>10 mg/dose</td>
<td>If Lo-Ovral or Norethindrone contraindicated</td>
</tr>
<tr>
<td>Alternative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Supplemental Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminocaproic acid (Amicar)</td>
<td>100 mg/kg IV x 1 loading dose, then 50 mg/kg IV Q6H</td>
<td>5 g/dose</td>
<td>Consult Hematology if using Amicar or Transexemic acid</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>10 mg/kg IV Q8H</td>
<td>600 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Ondansetron (Zofran)</td>
<td>0.15 mg/kg PO or IV Q8H</td>
<td>8 mg/dose</td>
<td>If IV or oral hormone therapy given, Zofran and Zantac needed for nausea</td>
</tr>
<tr>
<td>Ranitidine (Zantac)</td>
<td>1 mg/kg IV Q8H</td>
<td>50 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Ferrous Sulfate (Iron)</td>
<td>325 mg (65 mg elemental iron) PO BID</td>
<td>325 mg/dose</td>
<td>If Hgb &lt;10, start once tolerating PO</td>
</tr>
<tr>
<td>Docusate (Colace)</td>
<td>50-100 mg QD</td>
<td>100 mg/dose</td>
<td>If iron given</td>
</tr>
</tbody>
</table>
Follow-up

**FIRST VISIT (ADMIT/ED or OUTPT)**
- Utilize Heavy Menstrual Bleeding Epic pathway for ED visits
- Phillip Screening tool
- PBAC (download HFA menstrual bleeding app)

**First Tier labs:**
- **Hematologic tests:** CBC with reticulocyte count, peripheral blood smear for platelet morphology, +/- iron profile
- **Endocrine tests:** FT4, TSH
- **Gynecologic tests:** Pregnancy test, pelvic ultrasound (rarely done)
- **Blood bank:** ABO blood group
- **Coagulation tests:** PT, aPTT, fibrinogen, TT and VWD profile (VWF Ag, FVIII:C, VWF: RCo)

**SECOND VISIT (4-12 weeks later)**
- Verify Phillip screening tool done
- PBAC (document prior to and last 2 months)

**Repeat testing:**
- VWD profile (VWF Ag, FVIII:C, VWF: RCo)
- CBC with diff, retic
- Review VWD algorithm if VWF:Ag, FVIII:C or VWF:RCo <50

**THIRD VISIT (2-12 weeks later)**
- If VWF profile negative twice and other coagulation studies normal then proceed with Platelet aggregation testing
- If ATP release reduced then order Platelet EM
- Review VWD algorithm if VWF:Ag, FVIII:C or VWF:RCo <50

**ADDITIONAL CONSIDERATIONS (select cases)**
- **Endocrine tests:** prolactin, FSH, LH, free testosterone, DHEAS (if suspicion of PCOS)
- **Liver Function tests:** CMP (with prolonged P and normal FVII)
- **Additional VWD testing:** VWF multimers: VWF:CB, Exon 28 analysis (D1472H)
- **Thromboelastography:** If available
- **Coagulant factor assays:** If aPTT prolonged then send FIX, FXI, FVIII, FXII
- **Platelet glycoprotein expression/ flowcytometry:** based on platelet aggregation testing

Adapted from Ayesha Zia algorithm
Strategies addressing HMB in adolescents

• Creation of combined women’s bleeding disorder clinic
  – Multi-disciplinary clinic once a month at Emory University Gyn clinic and once a month at Egleston

• Create clinical pathway for adolescent girls with heavy menstrual bleeding
  – Unified diagnostic and management algorithm

• Clinical trials and studies
  – EHF products in hemophilia carriers
  – DDAVP in Carriers
  – ATHENA study (ATHN Dream award)
DDAVP in Hemophilia A carriers study

- **Hypothesis:** The bleeding tendency in hemophilia A carriers is due to a reduced ability to elevate and sustain FVIII and VWF levels compared to normal women.

- **Design:** Cross-sectional study in which adult hemophilia A carriers are given IV DDAVP, to evaluate “Stress” response over 6 hours compared to controls.

<table>
<thead>
<tr>
<th></th>
<th>Hemophilia A Carriers (n=13)</th>
<th>Normal Controls (n=5*)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years (range)</td>
<td>37 (25-60)</td>
<td>20 (18-22)</td>
<td>0.0002</td>
</tr>
<tr>
<td>% Blood Type O</td>
<td>66.6 (n=9)</td>
<td>60</td>
<td>0.821</td>
</tr>
<tr>
<td>Median ISTH BAT Bleeding Score (range)</td>
<td>8 (0-17)</td>
<td>1 (0-4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Median Baseline FVIII Level, IU/mL (range)</td>
<td>0.57 (0.31-1.25)</td>
<td>1.15 (0.82-1.98)</td>
<td>0.056</td>
</tr>
<tr>
<td>Median Baseline VWF:Ag, IU/mL (range)</td>
<td>0.87 (0.5-1.68)</td>
<td>0.67 (0.55-1.24)</td>
<td>0.374</td>
</tr>
<tr>
<td>Median Baseline VWF Activity, IU/mL (range)</td>
<td>0.59 (0.39-1.66)</td>
<td>0.61 (0.48-1.06)</td>
<td>0.979</td>
</tr>
<tr>
<td>Median Baseline VWFpp:Ag Ratio (range)</td>
<td>1.00 (0.6-1.5)</td>
<td>1.55 (1.2-1.9)</td>
<td>0.024</td>
</tr>
</tbody>
</table>
**DDAVP in Hemophilia A carriers study**

<table>
<thead>
<tr>
<th></th>
<th>Hemophilia A Carriers (n=13)</th>
<th>Normal Controls (n=4)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FVIII</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Change in FVIII, IU/mL (range)</td>
<td>0.85 (0.62-1.92)</td>
<td>2.31 (2.16-3.42)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Median Maximum Fold Change in FVIII (range)</td>
<td>1.79 (0.68-2.82)</td>
<td>2.01 (1.73-2.63)</td>
<td>0.245</td>
</tr>
<tr>
<td>Median Fold Change in FVIII at 4 hours (range)</td>
<td>0.93 (0.21-2.18)</td>
<td>1.67 (1.28-2.06)</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>VWF:Ag</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Change in VWF:Ag, IU/mL (range)</td>
<td>0.86 (0.76-1.30)</td>
<td>0.87 (0.68-1.90)</td>
<td>0.763</td>
</tr>
<tr>
<td>Median Maximum Fold Change in VWF:Ag (range)</td>
<td>1.11 (0.46-1.56)</td>
<td>1.37 (0.94-1.94)</td>
<td>0.245</td>
</tr>
<tr>
<td>Median Fold change in VWF:Ag at 4 hours (range)</td>
<td>0.74 (0.35-1.30)</td>
<td>1.21 (0.78-1.51)</td>
<td>0.043</td>
</tr>
<tr>
<td><strong>VWF Activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Change in VWF Activity, IU/mL (range)</td>
<td>1.06 (0.66-1.50)</td>
<td>1.21 (0.76-1.29)</td>
<td>0.639</td>
</tr>
<tr>
<td>Median Maximum Fold Change in VWF Activity (range)</td>
<td>1.66 (0.83-2.44)</td>
<td>1.93 (1.58-2.49)</td>
<td>0.285</td>
</tr>
<tr>
<td>Median Fold Change in VWF Activity at 4 hours (range)</td>
<td>1.20 (0.72-1.82)</td>
<td>1.67 (1.46-1.89)</td>
<td>0.035</td>
</tr>
</tbody>
</table>
ATHENA

• ATHN Dream Award (July 2017)
  – A cross-sectional observational study of females with bleeding disorders enrolled in the ATHNdataset (2 years)

  – Aim 1: To characterize the population of women with bleeding disorders.

  – Aim 2: To create an enrichment dataset focused on reproductive tract bleeding in order to characterize bleeding symptoms specific to the population of women with bleeding disorders.

  – Aim 3: To characterize the impact of HMB and the treatment strategies for HMB in women with bleeding disorders.
Children's Healthcare of Atlanta | Emory University

EHF products in Symptomatic Adult Hemophilia A carriers

- Hypothesis: The use of a single dose of extended half-life rFVIII:Fc or rFIX:Fc product in 16 symptomatic hemophilia A and B carriers will lead to a clinically significant reduction in menstrual bleeding as measured by Pictorial Bleeding Assessment Chart (PBAC).

- Study design: Prospective study. We will enroll 16 adolescent and adult symptomatic female hemophilia A or B carriers with a baseline FVIII or FIX activity of ≤60% at the time of recruitment over a 2 year time period at a single institution.