Females with Bleeding Disorders: Ongoing initiatives and research.

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State Hemophilia Meeting

HTRS MRA and HOG Clinical Scientist

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Children's℠
Healthcare of Atlanta

EMORY
UNIVERSITY

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?

Philipp CS. *Am J Obstet Gynecol* 2011
www.cdc.gov
www.wfh.org

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

- **<u>Predictive of heavy menstrual bleeding</u>**
  - 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

The numbers 1-8 represent the consecutive days of your menstrual period. Please record for each day, the number of pads you used that match each illustration.

	Pad	1	2	3	4	5	6	7	8
1 point									
5 points									
20 points									
	Clots (Yes/No)								

The numbers 1-8 represent the consecutive days of your menstrual period. Please record for each day, the number of tampons you used that match each illustration.

	Tampon	1	2	3	4	5	6	7	8
1 point									
5 points									
10 points									
	Clots (Yes/No)								

Case:
Pictorial Bleeding Assessment Chart

- **PBAC score**
  - (6 x 5) + (20 x20)
  - **430**
  - **>100** correlates with ~80cc/cycle
    - 86% sens. and 89% spec.
  - **≥185** able to discriminate between VWD and normals

The numbers 1-8 represent the consecutive days of your menstrual period. Please record for each day, the number of pads you used that match each illustration.

	Pad	1	2	3	4	5	6	7	8
1 point									
5 points							3	3	
20 points		4	4	4	4	4			
	Clots (Yes/No)								

The numbers 1-8 represent the consecutive days of your menstrual period. Please record for each day, the number of tampons you used that match each illustration.

Tampon	1	2	3	4	5	6	7	8
Clots (Yes/No)								

Higham et al. BJH 1990
Siboni HM et al. Haemophilia 2009
Revel-Vilk S et al. Jpeds 2012

BLOODSISTERHOOD

A NEW APP FOR WOMEN WITH BLEEDING DISORDERS!

DOWNLOAD FOR FREE!

- 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

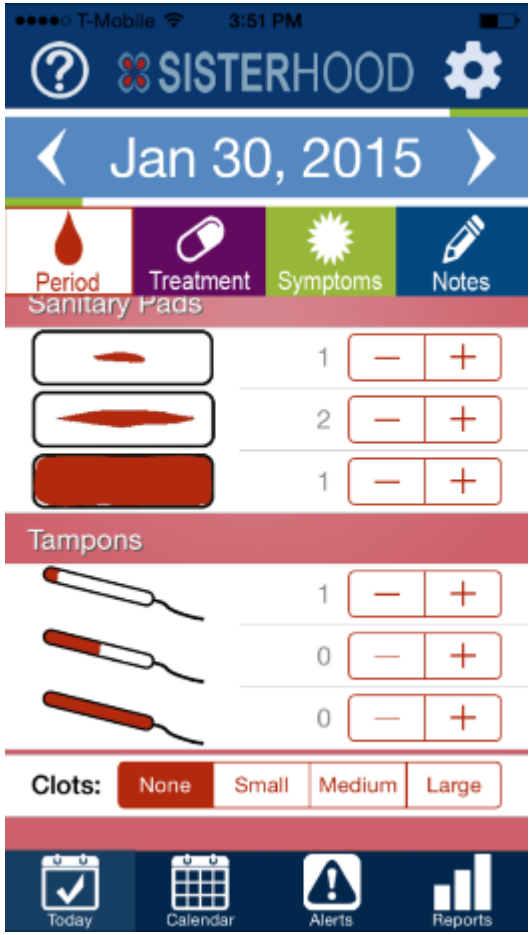
HFA Hemophilia Federation of America

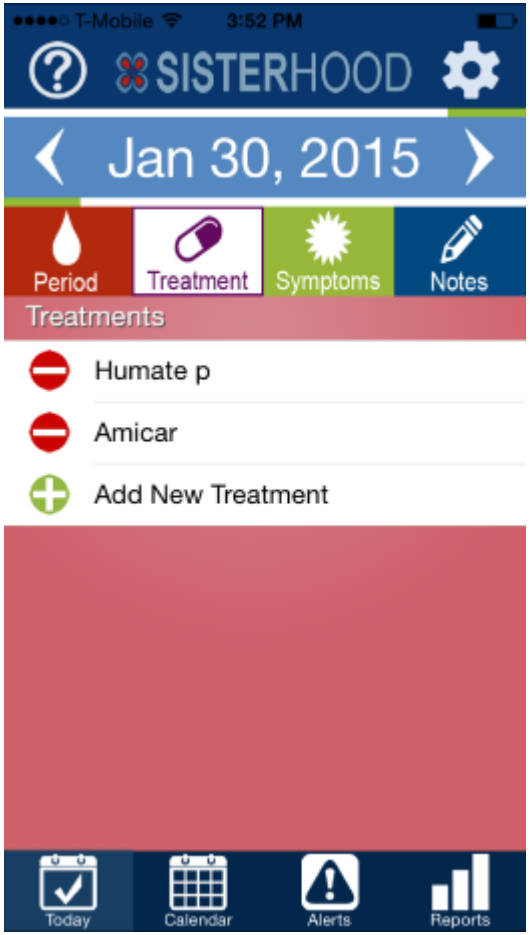
Available on the App Store

ANDROID APP ON Google play

hemophiliafed.org

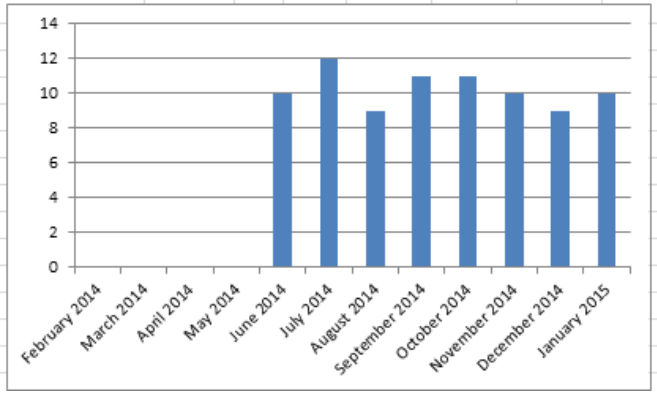
Menstrual diary app





Monthly Tracking

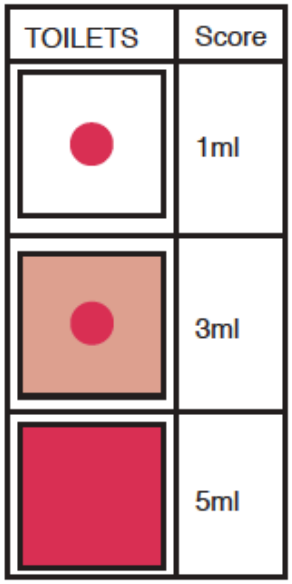
Month	Days Bled	Days	%
February 2014	0	28	0%
March 2014	0	31	0%
April 2014	0	30	0%
May 2014	0	31	0%
June 2014	10	30	33%
July 2014	12	31	39%
August 2014	9	31	29%
September 2014	11	30	37%
October 2014	11	31	35%
November 2014	10	30	33%
December 2014	9	31	29%
January 2015	10	31	32%



Updates coming early March 2017

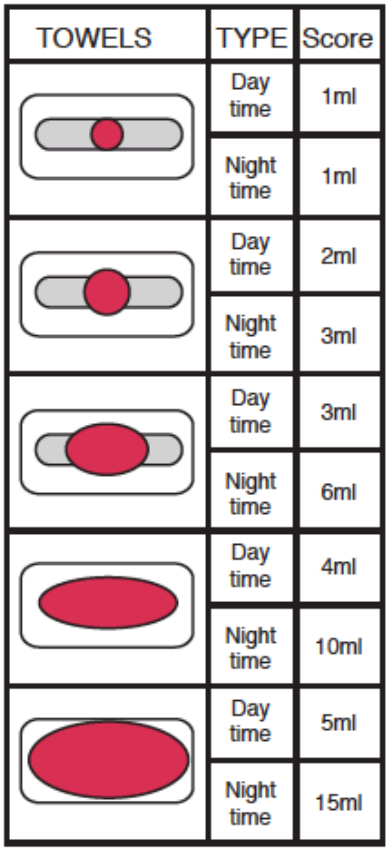
Updates

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

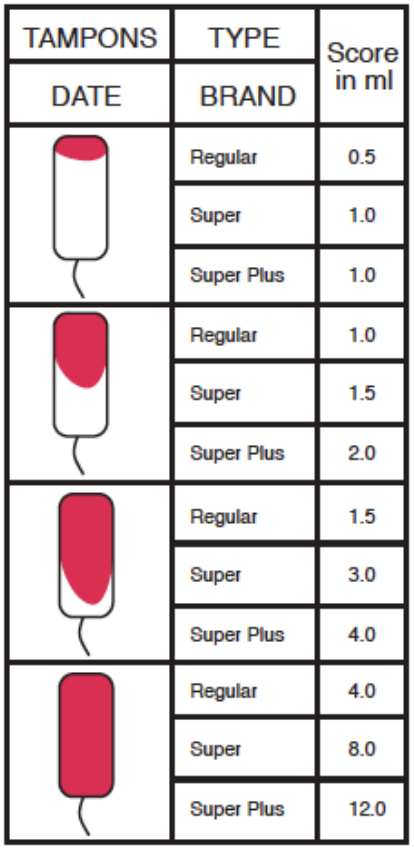


TOILETS	Score
	1ml
	3ml
	5ml

CLOTS	Score
	1ml
	3ml
	5ml



TOWELS	TYPE	Score
	Day time	1ml
	Night time	1ml
	Day time	2ml
	Night time	3ml
	Day time	3ml
	Night time	6ml
	Day time	4ml
	Night time	10ml
	Day time	5ml
	Night time	15ml



TAMPONS	TYPE	Score in ml
DATE	BRAND	
	Regular	0.5
	Super	1.0
	Super Plus	1.0
	Regular	1.0
	Super	1.5
	Super Plus	2.0
	Regular	1.5
	Super	3.0
	Super Plus	4.0
	Regular	4.0
	Super	8.0
	Super Plus	12.0

Case

- How do you decide what level (if any) of hemostatic investigation is warranted?

Established guideline in need of validation

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

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

Review

Evaluation and management of acute menorrhagia in women with and without underlying bleeding disorders: consensus from an international expert panel

Andra H. James [a,*], Peter A. Kouides [b], Rezan Abdul-Kadir [c], Jennifer E. Dietrich [d], Mans Edlund [e], Augusto B. Federici [f], Susan Halimeh [g], Pieter Willem Kamphuisen [h], Christine A. Lee [i], Oscar Martínez-Perez [j], Claire McLintock [k], Flora Peyvandi [l], Claire Philipp [m], Jeffrey Wilkinson [n], Rochelle Winikoff [o]

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

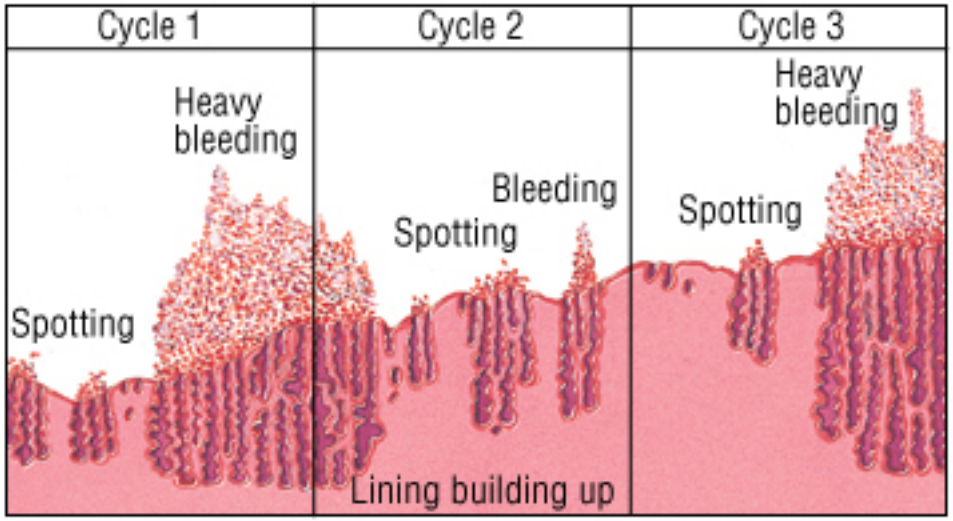
Cause	Age 13-19	Age 20-34	Age 35-49	Age 50+
Adolescent anovulation	→			
Bleeding disorder	→	→	→	→
Local pathology			→	→
New systemic disease		→	→	→
Anticoagulant therapy	→	→	→	→
Post-op complication			→	→
Hypothyroidism		→	→	→
Peri-menopausal anovulation			→	→

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.



"DUB" Harvard Health Publications

Heavy menstrual bleeding

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

Bleeding Disorder	Prevalence in women and teenage girls
von Willebrand disease	10% (4-36%)
Platelet dysfunction	20% (2-44%)
FXI deficiency	1-2%
Low FVIII (factor 8)	8%
Low platelets	5%
Rare factor deficiencies	<1%

Kadir et al. Lancet 1998
Dilley A et al. Obstet Gynecol 2001
Philip et al. J Thromb Haemost 2003
James AH et al. Am J Obtet Gynecol 2004
Edlund M et al. Am J Hematol 1996
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 progrestins (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-ogestrel, Loestrin
  - Consider COC with anti-androgenic progestins if acne is an issue
    - Norgestimate or drosperinone
      - 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)

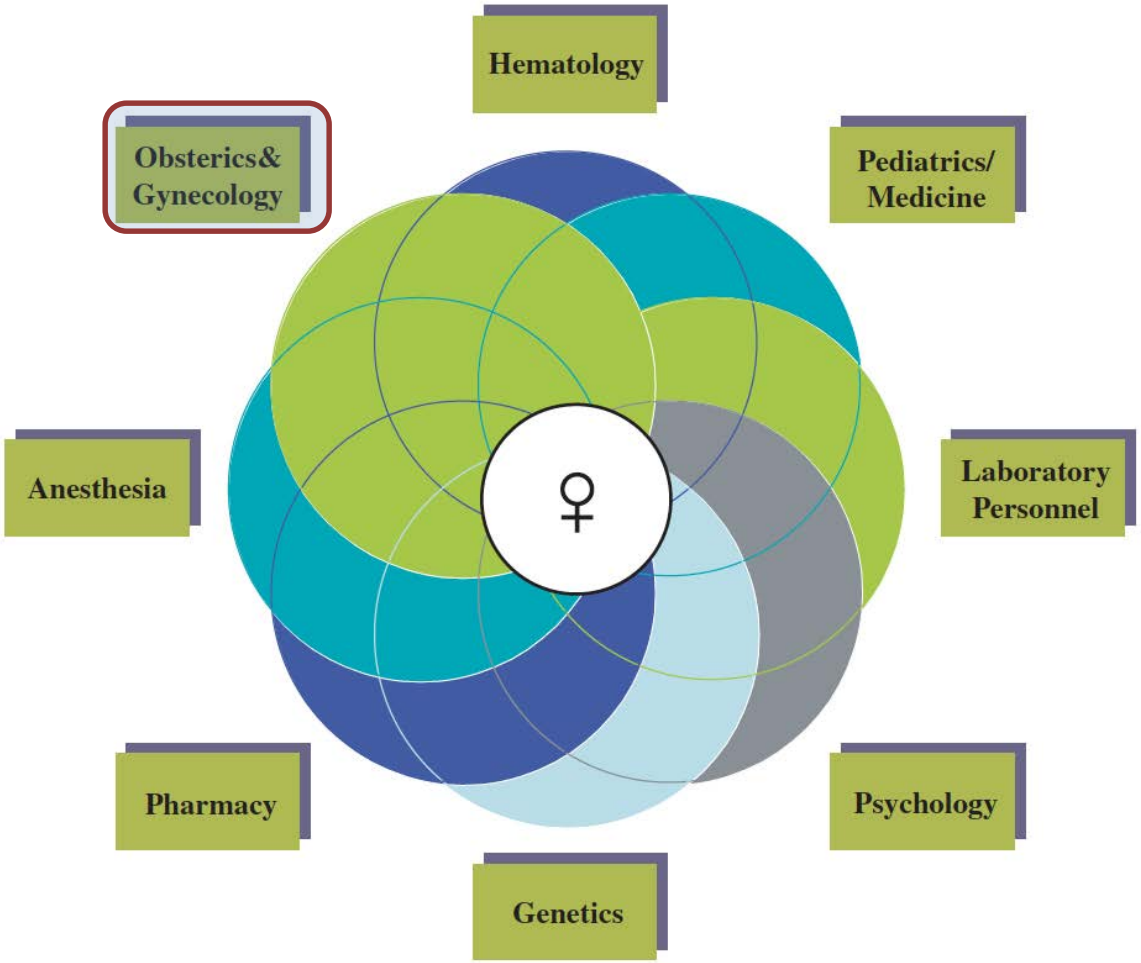
Multidisciplinary clinic

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

- 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
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  - Unified diagnostic and management algorithm
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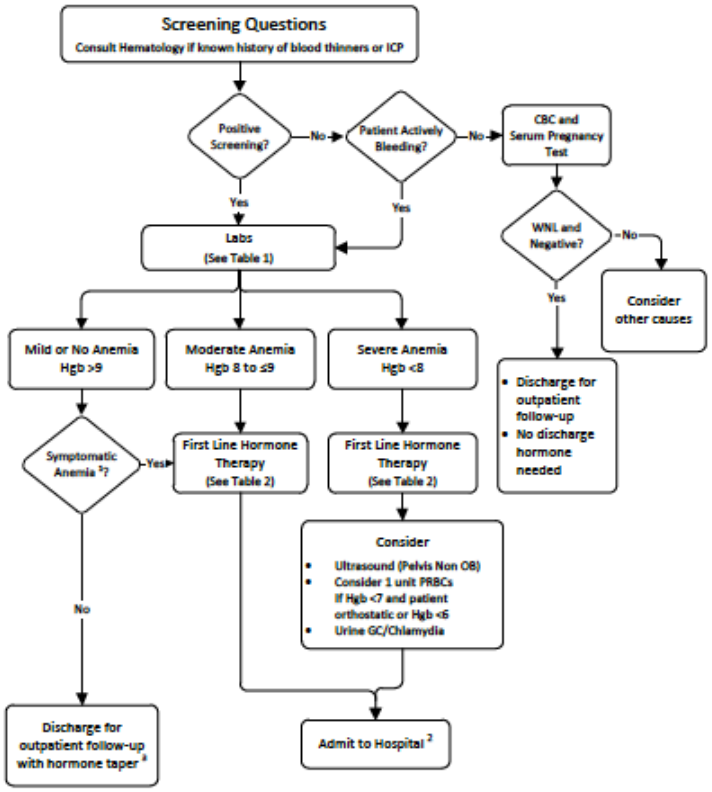
Strategies addressing HMB in adolescents

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

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
- If unstable/ hypotension, consider PICU transfer

[3] Discharge Instructions

- See Table 2 for discharge meds
- Hormone taper until daily regimen achieved. If bleeding recurs before daily regimen achieved, go back to prior dose. Skip placebo for 2 months
- Follow-up with a Gynecologist, in the Emory Fellows Family Planning/ Gynecology Clinic (404.778.3401), or in the Hughes Spalding Adolescent Medicine Clinic (404.785.9558) in 1-2 weeks
- Follow-up with the Hematology Clinic (404.785.1319) in 4-8 weeks to complete bleeding disorder workup
- Iron supplementation if indicated and encourage iron rich foods

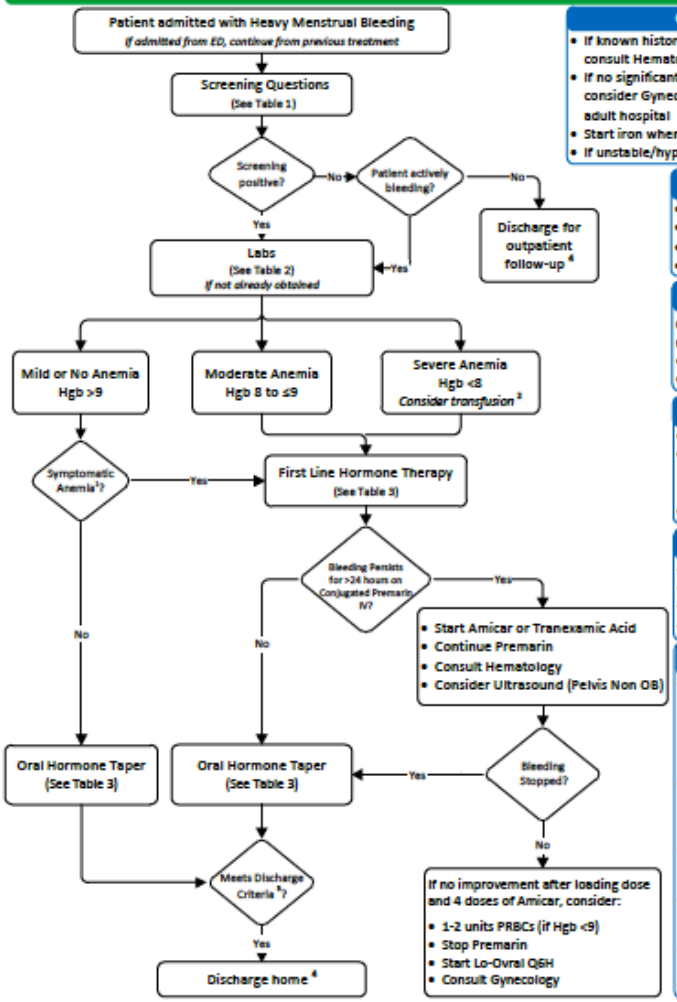
Developed through the efforts of Children's Healthcare of Atlanta and physicians on Children's medical staff in the interest of advancing pediatric healthcare. This is a general guideline and does not represent a professional care standard governing providers' obligation to patients. Ultimately the patient's physician must determine the most appropriate care. © 2016 Children's Healthcare of Atlanta, Inc.

Heavy Menstrual Bleeding Clinical Practice Guideline
Inpatient Management

DRAFT 4/19/16 Page 1 of 2

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

Algorithm



Considerations

- If known history of blood thinners or ICP, consult Hematology
- If no significant improvement after 48 hours, consider Gynecology consult and transfer to adult hospital
- Start iron when patient tolerating PO
- If unstable/hypotension, consider PICU transfer

[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 if bleeding or tachycardic
- Start IV if indicated

[3] Discharge Criteria

- Tolerating PO
- On room air
- No longer bleeding
- No longer orthostatic

[4] Discharge Instructions

- Follow-up with Gynecologist in Emory Fellows Family Planning/ Gynecology Clinic (404.778.3401), or Hughes Spalding Adolescent Medicine Clinic (404.785.9558) in 1-2 weeks
- Follow-up with the Hematology Clinic (404.785.1319) in 4-8 weeks to complete bleeding disorder work-up
- Continue hormone taper until daily regimen achieved. Skip placebo pills for two months
- If bleeding recurs, before daily regimen achieved, go back to prior dose
- Consider iron supplementation and encourage iron rich foods
- Keep menstrual calendar

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

Order Sets

ED Guideline Heavy Menstrual Bleeding Manage My Version Last Reviewed Date 7/11/2016 10:57 AM Add Order

"Please remember to use and document your responses to the Heavy Menstrual Screening Tool"
It is available in the Epic Toolbar above the trackboard, "HMB".
After documenting the responses in this pop-up, use the dotphrase ".HMB2" to pull your responses into your note if you desire.
You can also document responses to the screening tool by using the dotphrase ".HMB"

Clinical Practice Guideline for ED Heavy Menstrual Bleeding

Initiate Guideline

- **Initiate Order**
  - ☑ Include Patient in ED HMB Guideline
    Routine • ONGOING starting Today at 1015 Until Specified

Nursing

- **Nursing**
  - ☐ Vital Signs
  - ☐ Vital Signs With Orthostatic Pulse and BP
    NOW
  - ☐ Insert And Maintain IV
    NOW

Consults

- **Consults**
  - ☐ Hematology Oncology Consult
  - ☐ Gynecology Consult

Lab

- **Laboratory**
  - ☐ CBC
    STAT, ONCE, Clinician Collect
  - ☐ Pregnancy Serum Qual
    STAT, ONCE
  - ☐ PT/PTT PANEL
  - ☐ Thrombin Time
    STAT, ONCE
  - ☐ Fibrinogen Activity
    STAT, ONCE
  - ☐ Iron + TIBC
    STAT, ONCE
  - ☐ TSH with Reflex T4Free
    STAT, ONCE
  - ☐ Von Willebrand Profile
    STAT, ONCE
  - ☐ Type and Screen
    STAT, ONCE
  - ☐ GC/Chlam by Amplification
    STAT, ONCE

Diagnostics

- **Radiology**
  - ☐ US PELVIS NON OB
    STAT, IMAGING ONCE

Heavy Menstrual Bleeding Medications

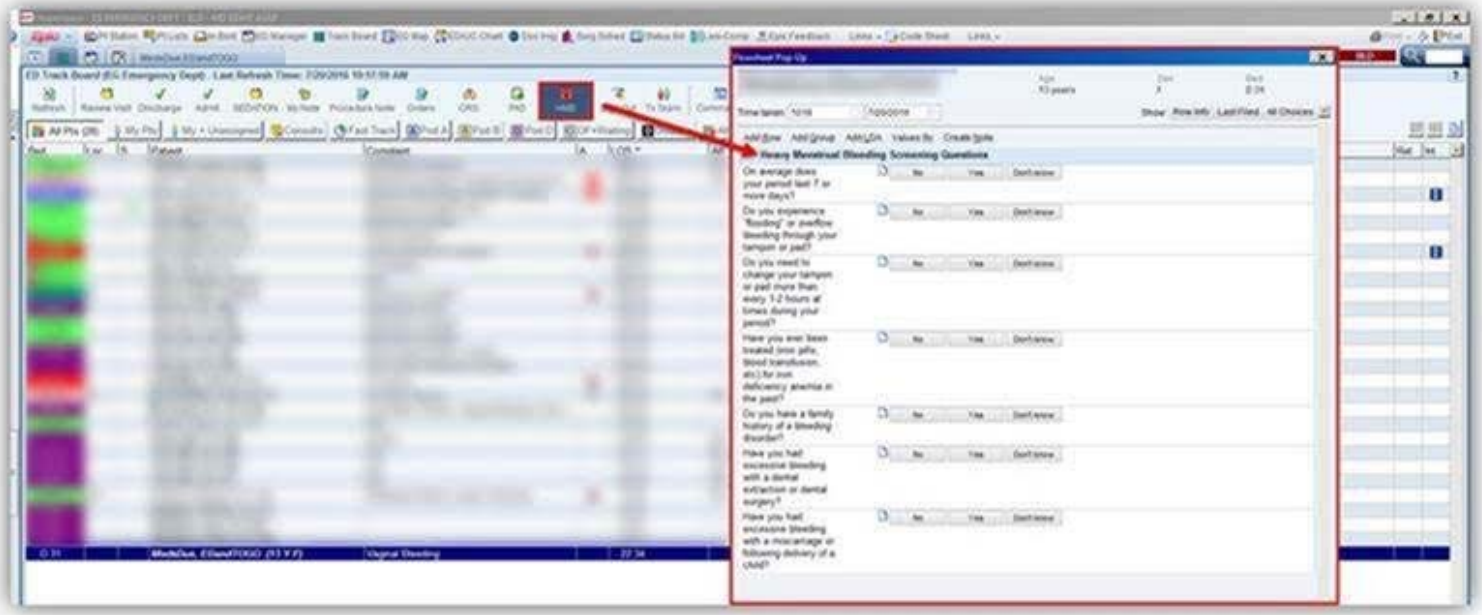
- **Hormone Therapy**
  - ☐ conjugated estrogens (PREMARIN) injection
    25 mg, IV, X1
  - ☐ NON-FORM ** Norethindrone Acetate tab
    5 mg, Oral, X1
  - ☐ medroxyPROGESTERone (PROVERA) tab
    10 mg, Oral, X1
- **Other Medications**
  - ☐ ranitidine (ZANTAC) injection solution
    1 mg/kg, IV, X1
  - ☐ ondansetron (ZOFRAN) injection solution
    0.15 mg/kg, IV, X1
  - ☐ ferrous sulfate (65 mg elemental iron)
    1 Tab, Oral, X1
  - ☐ docusate (COLACE) capsule
    50-100 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

	Human Milk Intake				
☑	Human Milk				
☑	**Output**				
☑	Elimination Status				
	Urine (mL)				
	Urinary Frequency				
	Emesis (mL)				
	Emesis Frequency				
	Stool (mL)				
	Stool Frequency				
	Menstrual Blood Loss Frequency			5	
	Menstrual Blood Loss Description			Heavy;C...	
	Intermittent GI/GU Procedures				
	Procedure				

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.

04/01/16 1359

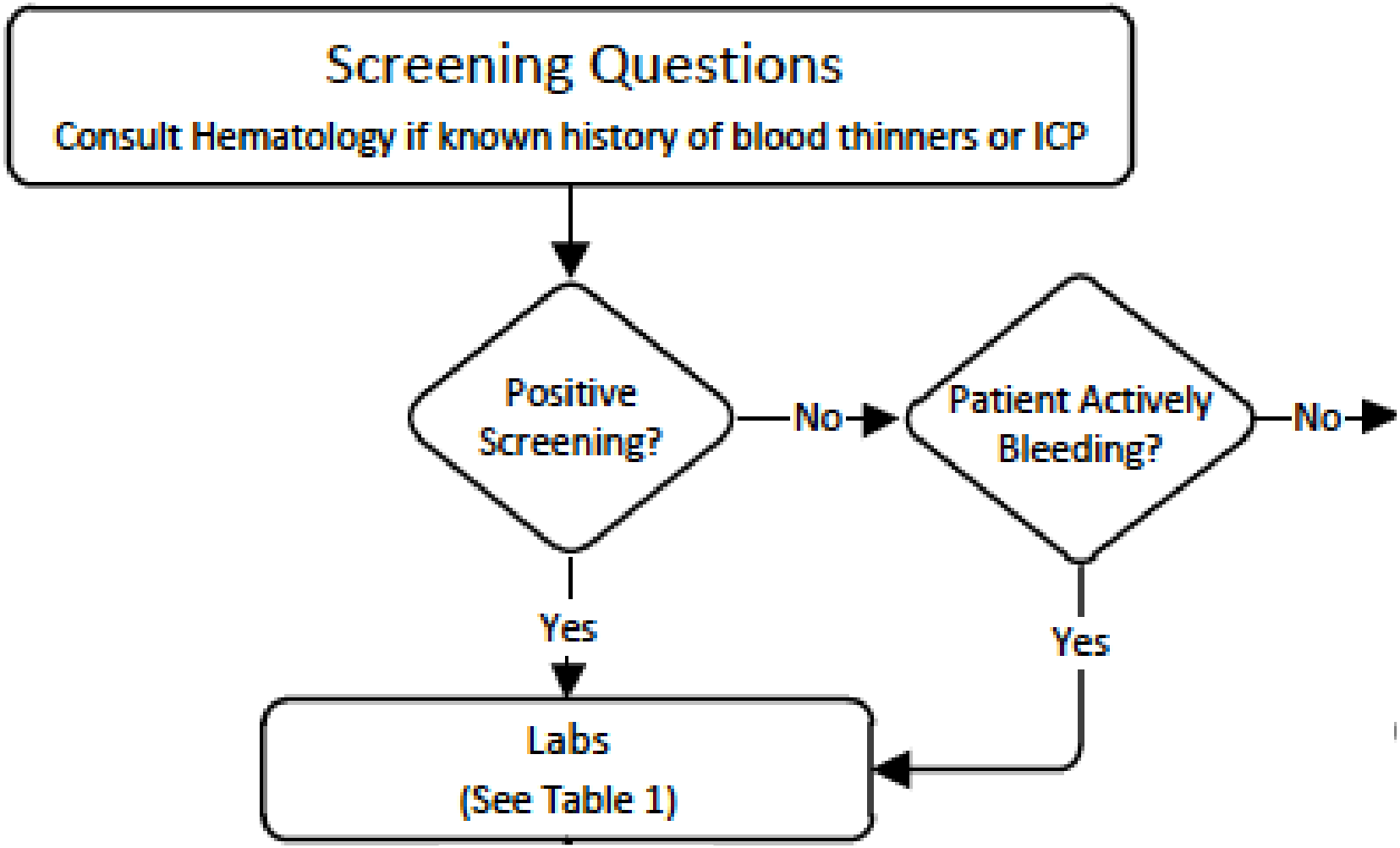
Menstrual Blood Loss Description

Select Multiple Options: (F5)

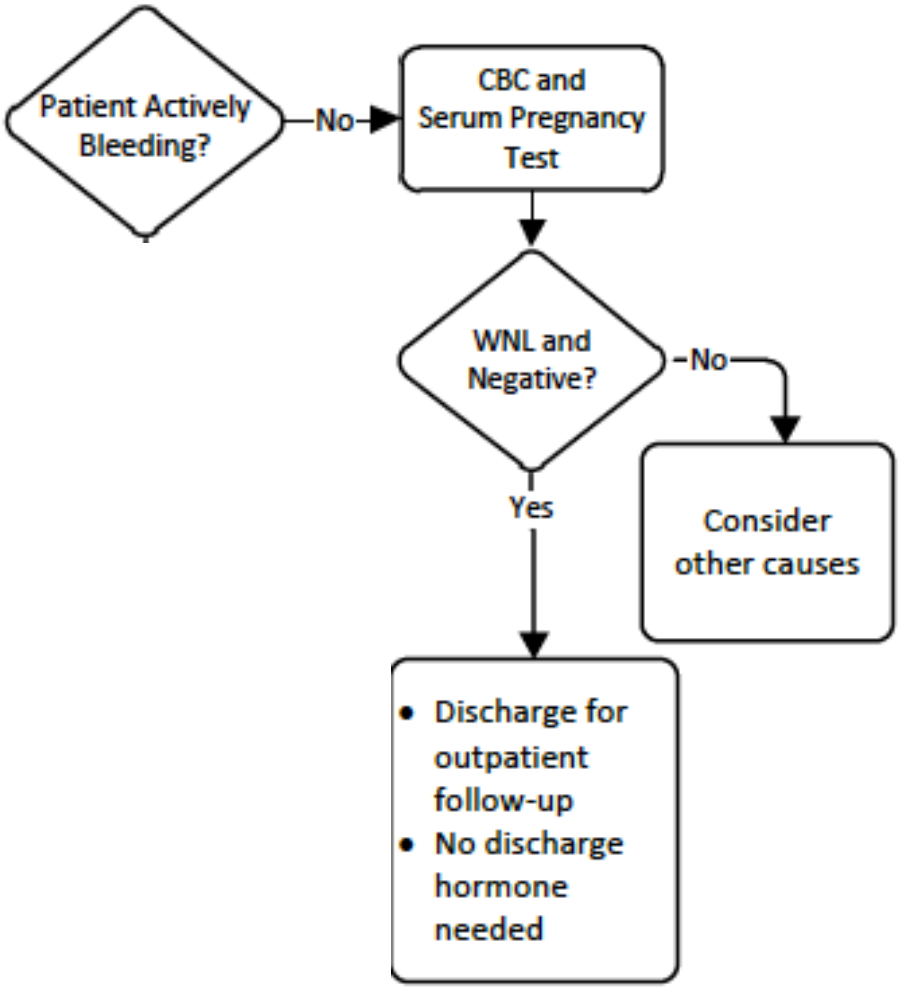
- Reported by patient/parent
- Spotting
- Light
- Moderate
- Heavy
- Brick
- Bright red
- Clots

Comment (F6)

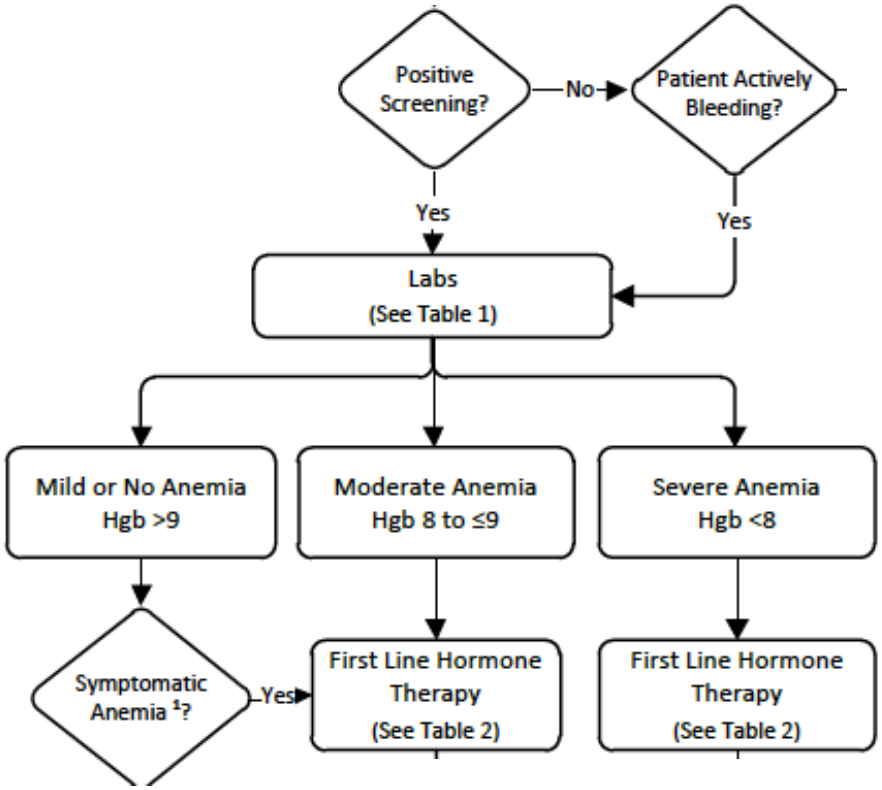
ED management



ED management



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)

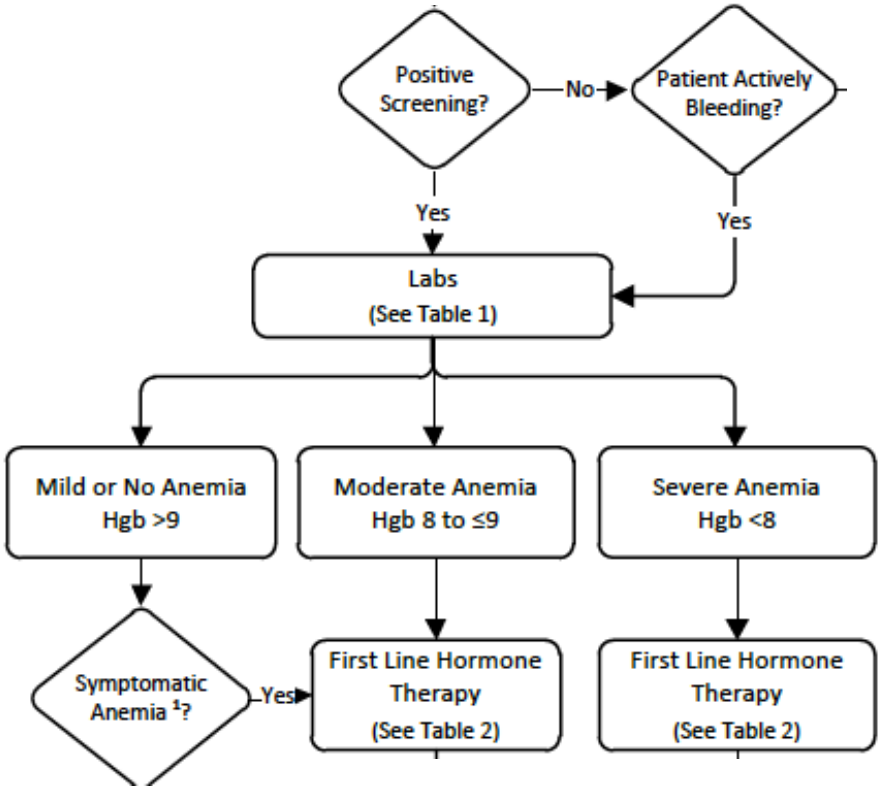
Consider: Ultrasound (Pelvis Non OB): If pain or concern for mass
Urine GC/Chlamydia: If concern for STI (Consider RPR and HIV)

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)

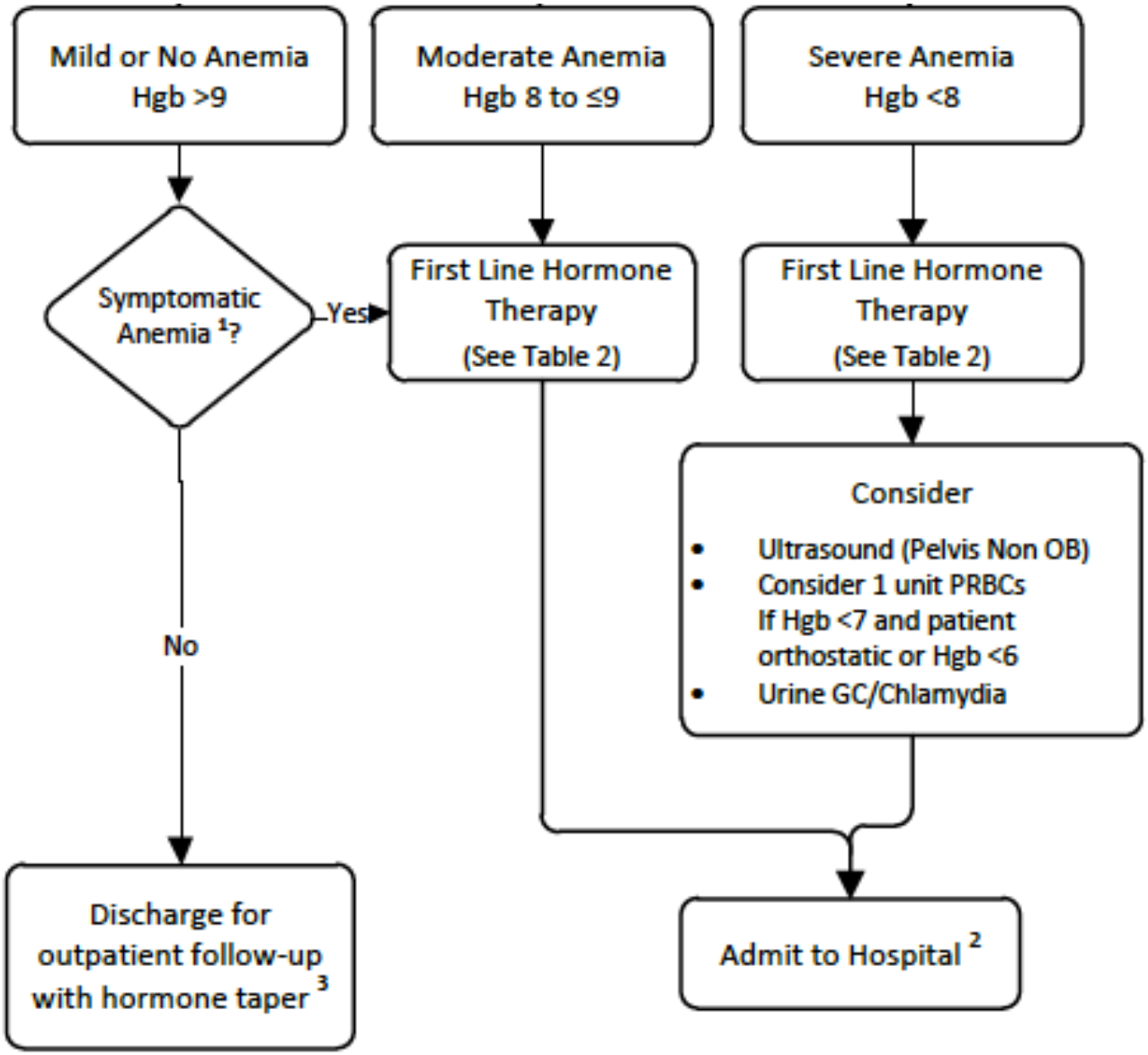
Abnormal labs resulting after discharge will be received by Transfer Center who will contact the Clinical Director of Hemostasis/Thrombosis

ED management



Medication	Dosage	Max Dose	Comments
First Line Hormone Therapy	*If already taking an oral combined oral contraceptive (COC), discontinue and begin the following therapy.*		
Conjugated Estrogens (Premarin) *Preferred*	25 mg IV x1, If bleeding continues consider repeating after 4 hours	25 mg/dose	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
Norethindrone *Alternative*	5 mg PO x1, If bleeding continues consider repeating after 4 hours	5 mg/dose	
Medroxyprogesterone *Alternative*	10 mg PO x1	10 mg/dose	If Conjugated Premarin or Norethindrone contraindicated

ED management



ED Medications

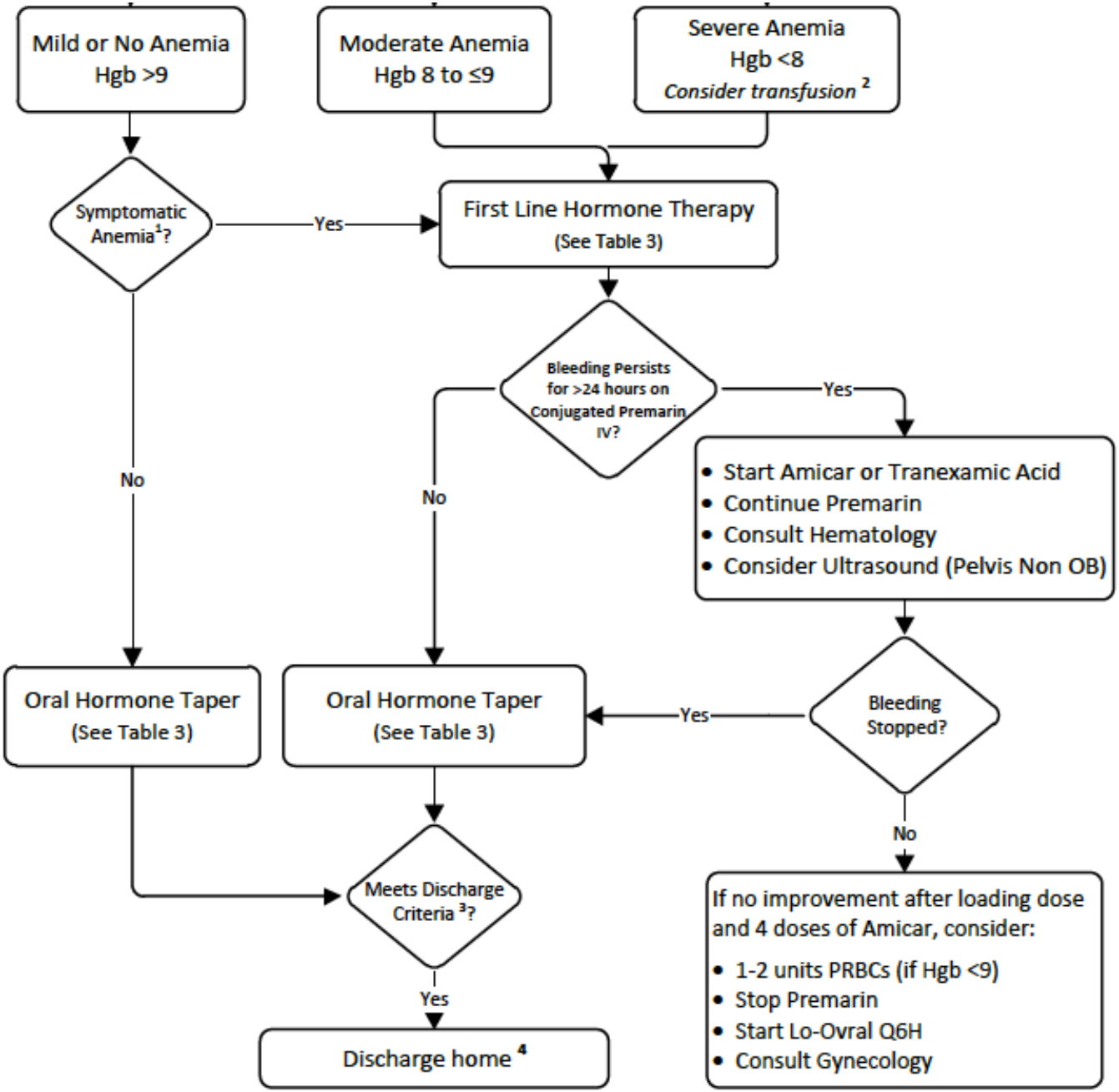
Table 1: ED Medications

Medication	Dosage	Max Dose	Comments
First Line Hormone Therapy	*If already taking an oral combined oral contraceptive (COC), discontinue and begin the following therapy.*		
Conjugated Estrogens (Premarin) *Preferred*	25 mg IV x1, If bleeding continues consider repeating after 4 hours	25 mg/dose	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
Norethindrone *Alternative*	5 mg PO x1, If bleeding continues consider repeating after 4 hours	5 mg/dose	
Medroxyprogesterone *Alternative*	10 mg PO x1	10 mg/dose	If Conjugated Premarin or Norethindrone contraindicated
Supplemental Medications			
Ferrous Sulfate	325 mg (65mg elemental iron) PO x1	325 mg/dose	If Hgb <10, start if tolerating PO
Docusate (Colace)	50-100 mg x1	100 mg/dose	If iron given
Ondansetron (Zofran)	0.15/mg/kg PO or IV x1	8 mg/dose	If IV or oral hormone therapy given
Ranitidine (Zantac)	1 mg/kg IV x1	50 mg/dose	If IV or oral hormone therapy given

Table 2: Discharge Medications

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

Inpatient management



Inpatient Medications

Table 1: Medication

Medication	Dosage	Max Dose	Comments
First Line Hormone Therapy	*If already taking a combined oral contraceptive (COC), discontinue and begin the following therapy.*		
Conjugated Estrogens (Premarin) *Preferred*	25 mg IV Q4H until bleeding stops	25 mg/dose	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
Norethindrone *Alternative*	5 mg PO Q4H until bleeding stops	5 mg/dose	
Medroxyprogesterone *Alternative*	10 mg PO Q6H	10 mg/dose	If Conjugated Premarin, Norethindrone, or Lo-Ovral contraindicated
Maintenance and Discharge Hormone Therapy			
Lo-Ovral *Preferred*	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	1 tab/dose	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
Norethindrone *Alternative*	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	5 mg/dose	
Medroxyprogesterone *Alternative*	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	10 mg/dose	If Lo-Ovral or Norethindrone contraindicated
Supplemental Medications			
Aminocaproic acid (Amicar)	100 mg/kg IV x1 loading dose, then 50 mg/kg IV Q6H	5 g/dose	Consult Hematology if using Amicar or Transexemic acid
Tranexamic acid	10 mg/kg IV Q8H	600 mg/dose	
Ondansetron (Zofran)	0.15 mg/kg PO or IV Q8H	8 mg/dose	If IV or oral hormone therapy given, Zofran and Zantac needed for nausea
Ranitidine (Zantac)	1 mg/kg IV Q8H	50 mg/dose	
Ferrous Sulfate (Iron)	325 mg (65 mg elemental iron) PO BID	325 mg/dose	If Hgb <10, start once tolerating PO
Docusate (Colace)	50-100 mg QD	100 mg/dose	If iron given

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/ flow-cytometery: 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.

	Hemophilia A Carriers (n=13)	Normal Controls (n=5*)	P Value
Median Age, years (range)	37 (25-60)	20 (18-22)	0.0002
% Blood Type O	66.6 (n=9)	60	0.821
Median ISTH BAT Bleeding Score (range)	8 (0-17)	1 (0-4)	0.008
Median Baseline FVIII Level, IU/mL (range)	0.57 (0.31-1.25)	1.15 (0.82-1.98) (n=4)	0.056
Median Baseline VWF:Ag, IU/mL (range)	0.87 (0.5-1.68)	0.67 (0.55-1.24) (n=4)	0.374
Median Baseline VWF Activity, IU/mL (range)	0.59 (0.39-1.66)	0.61 (0.48-1.06) (n=4)	0.979
Median Baseline VWFpp:Ag Ratio (range)	1.00 (0.6-1.5) (n=6)	1.55 (1.2-1.9) (n=4)	0.024

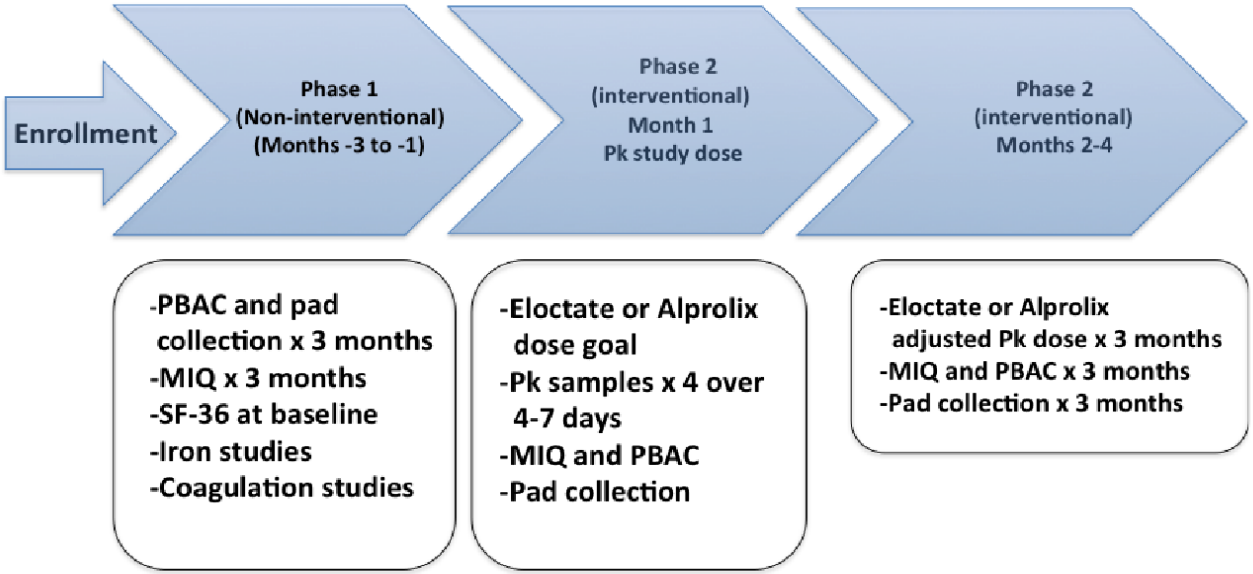
DDAVP in Hemophilia A carriers study

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

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.**

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.