The Evidence Based Approach to the Management of Acute AUB

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Disclosures

- None

Objectives

- Define Acute Abnormal Uterine Bleeding (AUB)
- Briefly review the etiologies & workup of acute AUB
- Review the evidence for medical management of acute AUB

Acute Abnormal Uterine Bleeding

- Defined as an episode of heavy bleeding, that in the opinion of the clinician, is of sufficient quantity to require immediate intervention to prevent further blood loss

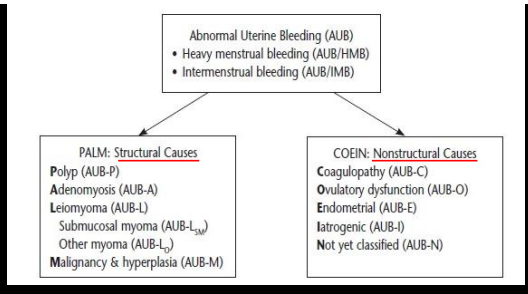
Assessment of the Patient with Acute AUB

#1: Evaluate for signs of hypovolemia & potential hemodynamic instability

#2: If unstable or hypovolemic, establish appropriate IV access

#3: Evaluate for the most likely etiology

FIGO International Federation of Gynecology and Obstetrics



Diagnosis of abnormal uterine bleeding in reproductive-aged women. Practice Bulletin No. 128. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2012;120:197–206.

Workup of Acute AUB

- Thorough history
  - Focus on:
    - Details of the current bleeding episode
    - Related symptoms
    - Past menstrual, gyn, medical history
  - Ask about medications or herbal remedies
    - Warfarin, Heparin, OCP's
    - Ginkgo, Ginseng, Motherwort

Workup of Acute AUB

- Thorough history
  - Up to 20% of women presenting with HMB will have an underlying bleeding disorder
  - May include:
    - vonWillebrand Disease
    - Other coagulation factor deficiencies
    - Hemophilia
    - Leukemia
    - Liver Failure

Disorder of Hemostasis in the Patient With Excessive Menstrual Bleeding

Initial screening for an underlying disorder of hemostasis in patients with excessive menstrual bleeding should be structured by medical history (positive screen comprises any of the following): *

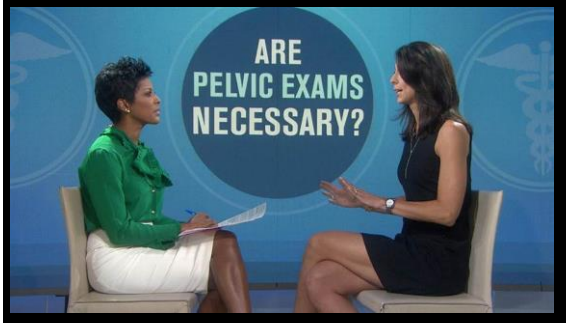
Heavy menstrual bleeding since menarche

One of the following:
- Postpartum hemorrhage
- Surgery-related bleeding
- Bleeding associated with dental work

Two or more of the following symptoms:
- Bruising one to two times per month
- Epistaxis one to two times per month
- Frequent gum bleeding
- Family history of bleeding symptoms

*Patients with a positive screen should be considered for further evaluation, including consultation with a hematologist and testing

Claessens EA, Cowell CA. Acute adolescent menorrhagia. *Am J Obstet Gynecol* 1981;139:277–80.

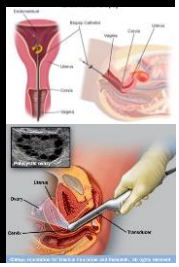


Workup of Acute AUB

- If screen positive for a history of a bleeding disorder…
  - Prothrombin
  - Partial thromboplastin time
  - +/- fibrinogen
  - vonWillebrand Testing
    - von Willebrand Ristocetin cofactor activity
    - von Willebrand factor antigen
    - Factor VIII

Workup of Acute AUB

- Based on clinical findings, other tests may be indicated:
  - hCG
  - Thyroid-stimulating hormone
  - Liver function tests
  - Workup for sepsis or leukemia
  - +/- Endometrial sampling
    - Age >45 years old
    - Age <45 with
      - Unopposed estrogen exposure
      - Failed medical management
      - Persistent AUB
  - +/- pelvic US



- Based on:
  - Clinical stability
  - Overall acuity
  - Suspected etiology
  - Desire for future fertility
  - Underlying medical problems

Objectives of Treatment

#1: to control the current episode of heavy bleeding

#2: to reduce menstrual blood loss in subsequent cycles

The Case

A 35 year old G4P2022 with a history of obesity (BMI 31) and pre-diabetes presents with complaints of heavy menstrual bleeding for the past 12 days. She also has complaints of dizziness. The patient reports her cycles are normally every 35 days that last for 7 days with moderate flow. However, with her current episode of bleeding, she is soaking through one pad every 2 hours. She is not currently sexually active.

The Case (continued)

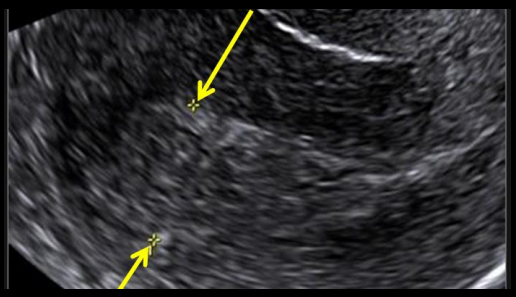
On exam:

BP 100/60 Pulse 115
Negative for orthostatic changes.

Pelvic Exam:
~ 50 mL of blood/clot in the vault
Active bleeding noted from the os
No cervical trauma or lesions or vaginal lacerations identified
No cervical motion tenderness or abnormal discharge noted
Uterus 8 weeks sized, no adnexal masses palpable

Labs  Hgb 8.9 Platelets 220 WBC 7

The Case (continued)



Which of the following medical therapies is/are FDA approved for acute AUB?

A. Levonorgestrel intrauterine device
B. Tranexamic Acid
C. Depo Provera
D. Intravenous conjugated equine estrogen

Intravenous estrogen results in which of the following:

A. Rapid growth of the endometrial epithelium and stroma
B. Vasospasm of uterine arteries
C. Increased platelet aggregation & capillary clotting
D. Increased Fibrinogen, Factor V &Factor XI
E. Increased production of both estrogen & progesterone receptors
F. All of the above

TRUE/FALSE?

When compared in a double-blind, randomized, placebo-controlled trial, 25mg of IV CEE was **more effective** in stopping vaginal bleeding at **3 hours** than placebo.

TRUE/FALSE?

When compared in a double-blind, randomized, placebo-controlled trial, 25mg of IV CEE was **more effective** in stopping vaginal bleeding at **5 hours** than placebo.

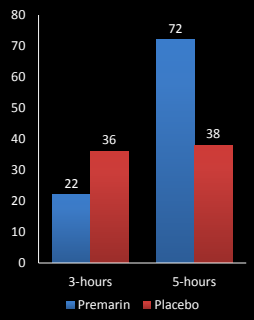
Use of Intravenous Premarin in the Treatment of Dysfunctional Uterine Bleeding- A Double Blind Randomized Control Study

DeVore GR, Owens O, Kase N.
Obstet Gynecol. 1982; 59(3):285-291.

- Placebo-controlled
- 17 patients in each group
- Mean baseline Hgb 12
- 25mg IV CEE given initially and then again at 3 hours
  - Bleeding Cessation rates evaluated at 3 & 5 hours

Bleeding Cessation Rates

- At 3 hours, placebo was more effective
- At 5 hours, rates of bleeding cessation with IV CEE was more effective
- Women with endometritis did not respond to therapy with IV CEE



Progesterone treats AUB by:

A. Stabilizing endometrial friability
B. Inhibiting endometrial growth by triggering apoptosis
C. Inhibiting angiogenesis
D. Stimulating conversion of estradiol to the less active estrone
E. All of the above

In a study comparing medroxyprogesterone acetate and oral contraceptives for the treatment of acute AUB, the **median number** of days to cessation of bleeding in **both groups** was:

A. 1 day
B. 2 days
C. 3 days
D. 4 days

Oral Medroxyprogesterone Acetate and Combination Oral Contraceptives (COC's) for Acute Uterine Bleeding: A Randomized Controlled Trial

Munro MG, Mainor N, Basu R, Brisinger M, Barreda L.
Obstet Gynecol. 2006;108(4):924-929.

- Eligibility Criteria:
  - Non-pregnant
  - Hemodynamically stable
  - Premenopausal women at least 18 years of age
  - Required emergent medical or surgical intervention
  - Hgb at least 8 g/dL
- Interventions:
  - Medroxyprogesterone acetate (MPA) 20 mg TID x 7 days
  - Norethindrone 1mg/ Ethinyl Estradiol (E2) 35 µg TID x 7 days
  - Both were followed by either dose above **once** daily, respectively, for 3 weeks
  - 20 patients in each group

Oral Medroxyprogesterone Acetate and Combination Oral Contraceptives for Acute Uterine Bleeding: A Randomized Controlled Trial

- Primary Outcome
  - The avoidance of unscheduled surgery in the 28 day follow-up period
- Additional outcomes:
  - Days to cessation of bleeding
  - Pad and tampon counts
  - Patient satisfaction scores
  - Degree of ancillary symptoms such as cramping & side effects associated with the meds (i.e. nausea/bloating)

Results

- All pts receiving MPA & 95% of OC patients avoided an unscheduled surgical procedure
  - One OC pt underwent a non-elective D&C for acute bleeding
- **Median** Number of days to cessation of bleeding in BOTH groups was 3 (*P*=.400)

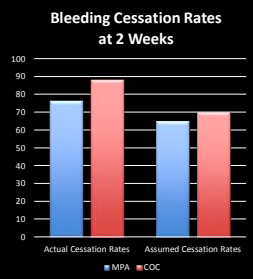


Table 3. Ancillary Symptoms and Treatment Side Effects

Symptom (Median of Average)	MPA	OCP	*P*
Bloating			
Baseline	0	0	.444
Week 1	0.00	0.00	.851
Week 2	0.00	0.00	.567
Cramping			
Baseline	1	1	.745
Week 1	0.00	0.43	.496
Week 2	0.00	0.00	.754
Nausea			
Baseline	0	0	.269
Week 1	0.00	0.57*	.710
Week 2	0.00	0.00	1.000

MPA, medroxyprogesterone acetate; OCP, oral contraceptive pill.
Scored from 0=none to 4=unbearable.
* Statistically significant compared with week 2 by signed rank test.

Patient Favorability

Percentage of patients that would use the treatment again	
Medroxyprogesterone Acetate	81
OCP's	69

Pitfalls of the Study

- No placebo group
- Heterogeneous group of patients
  - may be a strength of the study though since this reflects real-world scenarios
- Sample size was insufficient to demonstrate actual equivalence between the regimens
  - Though no statistically significant difference was shown
- Dosing decisions were based on textbook recommendations (expert opinion)

But what about the patients with contraindications to estrogen use?

A New Progestogen Only Medical Therapy For Outpatient Management of Acute, Abnormal Uterine Bleeding: A Pilot Study

Ammerman SR, Nelson AL.
Am J Obstet Gynecol. 2013;208(6):499.e1-5.

- Using results from the Munro trial…
  - Median time to bleeding cessation with high-dose oral medroxyprogesterone acetate (MPA) is 3 days
- … and pharmacologic data
  - Depot Medroxyprogesterone Acetate (DMPA) serum levels are therapeutic 3 days after injection
- The following regimen was developed:
  - DMPA 150 mg IM + MPA 20mg PO TID x 3 days

A New Progestogen Only Medical Therapy For Outpatient Management of Acute, Abnormal Uterine Bleeding: A Pilot Study

- Primary Outcomes
  1. Efficacy of the therapy in stopping uterine bleeding measured by:
     - Percentage of women who stopped bleeding
     - Mean time to bleeding cessation
     - Drop in Hgb
  2. Treatment Feasibility
  3. Tolerability
- Prospective, single-arm, pilot study

A New Progestogen Only Medical Therapy For Outpatient Management of Acute, Abnormal Uterine Bleeding: A Pilot Study

- Results
  - 48 women
  - All reported taking medication as directed
  - No patient lost to follow-up until after her bleeding had stopped
  - No surgical or additional medical treatments required during the 5 day study period
  - Mean time to bleeding cessation was 2.6 days

TABLE 3
Response to treatment by study day

Variable	Number of women (still) bleeding	Number of women who stopped bleeding in prior 24 h	Cumulative number of women who stopped bleeding	Percent of women who stopped bleeding	Mean number of sanitary protection products used in prior 24 h[a]
Baseline (day 0)	48	—	—	—	8.5
Day 1	36	12	12	25.0	2.0
Day 2	28	8	20	42.7	1.0
Day 3	14	14[b]	34	70.8	1.0
Day 4	9	5	39	81.3	1.0
Day 5	0	9[c]	48	100.0	0.0

[a] Number of products used by women who were still bleeding; [b] One woman was still spotting on day 3 but was lost to later follow-up; [c] Four women still had spotting but no longer required sanitary protection products.

Ammerman. New progestogen-only outpatient treatment for acute abnormal uterine bleeding. Am J Obstet Gynecol 2013.

TABLE 2
Baseline subject characteristics and baseline and day 3 hemoglobin values

Characteristic	Mean (SD)	Median	Range
Age, y	40.7 (9.35)	42.0	19–53
BMI, kg/m^2	34.9 (8.09)	33.0	21.5–51.2
Hemoglobin, baseline, g/dL	10.9 (1.58)	11.1	6.9–14.5[a]
Hemoglobin, day 3, g/dL	10.9 (1.62)	11.2	6.9–14.2[a]

[a] Hemoglobin on CBC was lower than the value from the point-of-care test (hemocue) used to determine the patient's eligibility for study participation.

Ammerman. New progestogen-only outpatient treatment for acute abnormal uterine bleeding. Am J Obstet Gynecol 2013.

Satisfaction	**Rating of 1-3 1, Poor 2, Good 3, Excellent**
Median Score	3
Mean Score	2.75
# of women ranking it a 1	0
% of patients that would recommend their treatment to a friend	100%

A New Progestogen Only Medical Therapy For Outpatient Management of Acute, Abnormal Uterine Bleeding: A Pilot Study

- Limitations
  - Single-arm, non-comparative pilot clinical trial
  - Only patients deemed eligible for outpatient management
  - Only studied short term response to therapy (5 days)
  - High satisfaction rate may be a reflection of receiving:
    - Treatment on site
    - Personal attention from one of the investigators

And then there's TXA…

Tranexamic Acid (TXA) Treatment for Heavy Menstrual Bleeding:
A Randomized Controlled Trial

Lukes AS, Moore KA, Muse KN, Gersten JK, Hecht BR, Edlund M, et al. *Obstet Gynecol* 2010;116:865-75.

- Double Blinded
- Randomized
- Adult women aged 18-49
  - History of Heavy Menstrual Bleeding
  - At least 60 mL in the initial pretreatment cycle & average of 80 mL over two pretreatment cycles
  - No obvious cervical or uterine pathology
    - Myomas allowed as long as not so significant to require surgery
- TXA 1.3 g TID (or at least 6 hours apart) for 5 days

Tranexamic Acid (TXA) Treatment for Heavy Menstrual Bleeding:
A Randomized Controlled Trial

- Primary Endpoints:
  - Mean reduction in menstrual blood loss with TXA that was:
    1. Significantly greater than in the placebo group
    2. Greater than 50 mL from the baseline
    3. Greater than a reduction in MBL that was perceived meaningful to women (36 mL)

Tranexamic Acid (TXA) Treatment for Heavy Menstrual Bleeding:
A Randomized Controlled Trial

- Results
  - 196 patients randomized
    - TXA 123
    - Placebo 73
  - Modified intent to treat
    - TXA 115
    - Placebo 72
  - Completed the study
    - TXA 94
    - Placebo 54

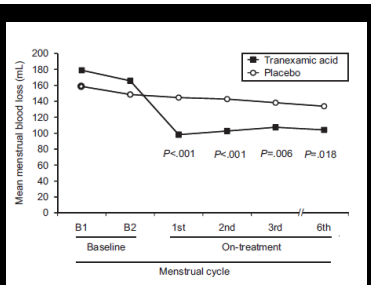
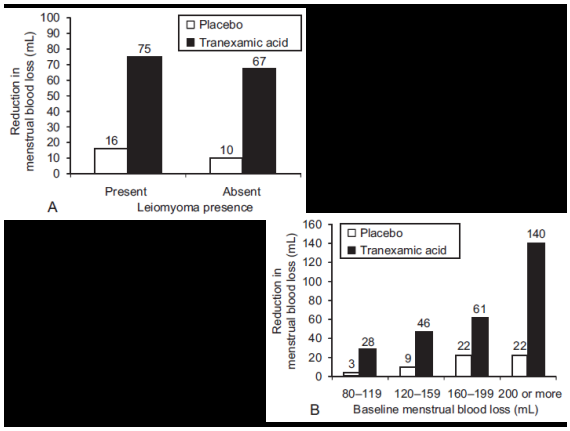
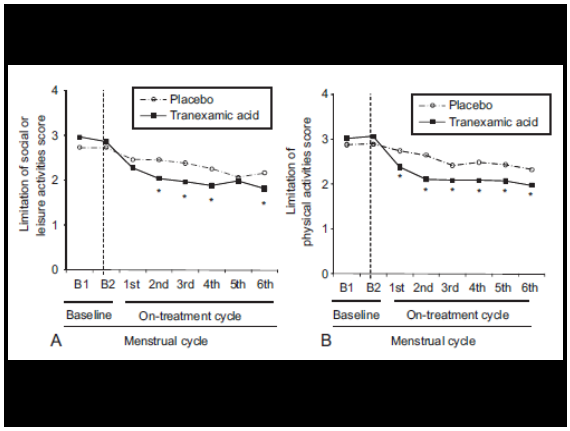
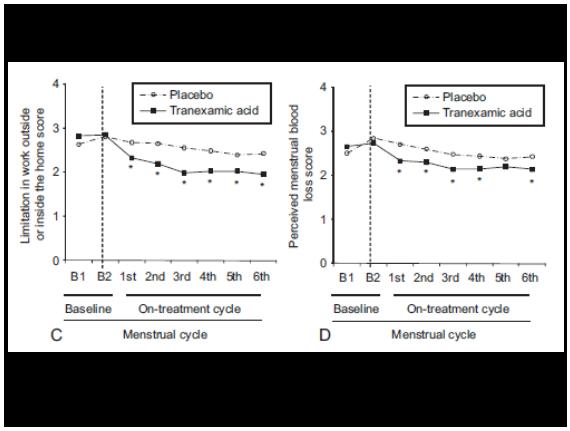


Fig. 2. Menstrual blood loss change over study course. Effects of tranexamic acid (n=115) and placebo (n=72) use on menstrual blood loss as measured by the alkaline hematin method are illustrated over the time course of the study. *P* values are for the comparison between tranexamic acid and placebo.

Lukes. Oral Tranexamic Acid for Heavy Menstrual Bleeding. Obstet Gynecol 2010.


Reduction in menstrual blood loss (mL)
Placebo
Tranexamic acid
16
75
10
67
Present
Absent
A
Leiomyoma presence
3
28
9
46
22
61
22
140
80–119
120–159
160–199
200 or more
B
Baseline menstrual blood loss (mL)


Limitation of social or leisure activities score
Limitation of physical activities score
Placebo
Tranexamic acid
B1
B2
1st
2nd
3rd
4th
5th
6th
Baseline
On-treatment cycle
A
Menstrual cycle
B
Menstrual cycle


Limitation in work outside or inside the home score
Perceived menstrual blood loss score
Placebo
Tranexamic acid
B1
B2
1st
2nd
3rd
4th
5th
6th
Baseline
On-treatment cycle
C
Menstrual cycle
D
Menstrual cycle

Tranexamic Acid (TXA) Treatment for Heavy Menstrual Bleeding:
A Randomized Controlled Trial

- Limitations:
  - Use of COX-2 inhibitors, NSAIDS and hormones prohibited during the menstrual/study cycle
  - Only studied patients with chronic HMB, not acute AUB
- Conclusions:
  - TXA was well tolerated
  - TXA significantly improved
    - Menstrual Blood Loss
    - Health-related quality of life

To Sum it Up

Drug	Dose	Schedule	Impact	Patient Favorability
IV Conjugated Equine Estrogen	25 mg IV	Q 4-6 hours x24 hours	⇩⇩	N/A
Medroxyprogesterone Acetate	20 mg PO	3x/day for 7 days	⇩⇩	☆☆
Combined Oral Contraceptives (Monophasic)	35 mcg of Ethinyl Estradiol	TID x 7 days	⇩⇩	☆
Medroxyprogesterone Acetate + IM Depot Medroxyprogesterone Acetate	DMPA 150 mg MPA 20 mg	Once TID x3 days	⇩⇩⇩	☆☆☆
Tranexamic Acid	1.3g PO	3x/day for 5 days	⇩⇩⇩ *	☆☆

Back to the Case

A 35 year old G4P2022 with a history of obesity (BMI 31) and pre-diabetes presents with complaints of heavy menstrual bleeding for the past 12 days. She also has complaints of dizziness. The patient reports her cycles are normally every 35 days that last for 7 days with moderate flow. However, with her current episode of bleeding, she is soaking through one pad every 2 hours. She is not currently sexually active.

The Case (continued)

On exam:

BP 100/60 Pulse 115
Negative for orthostatic changes.

Pelvic Exam:
~ 50 mL of blood/clot in the vault
Active bleeding noted from the os
No cervical trauma or lesions or vaginal lacerations identified
No cervical motion tenderness or abnormal discharge noted
Uterus 8 weeks sized, no adnexal masses palpable

Labs  Hgb 8.9 Platelets 220 WBC 7

The Case (continued)

- How would you treat her…
  - Assuming she is not currently contemplating a pregnancy?
  - Keeping in mind her BMI?

Things to keep in Mind…

- Be careful that the patient does not have contraindications to hormonal therapy
- Bleeding that does not respond to initial treatment requires additional investigation

In Conclusion

- Treatment of AUB first requires an evaluation for likely etiologies
  - Always perform a pelvic exam!
- Available treatment methods should be considered while being cognizant of possible contraindications
- Consider the patient's comorbidities and reproductive plans when deciding on a treatment method

References

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