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Management of Acute Abnormal Uterine Bleeding in Nonpregnant Reproductive-Aged Women

ABSTRACT: Initial evaluation of the patient with acute abnormal uterine bleeding should include a prompt assessment for signs of hypovolemia and potential hemodynamic instability. After initial assessment and stabilization, the etiologies of acute abnormal uterine bleeding should be classified using the PALM–COEIN system. Medical management should be the initial treatment for most patients, if clinically appropriate. Options include intravenous conjugated equine estrogen, multi-dose regimens of combined oral contraceptives or oral progestins, and tranexamic acid. Decisions should be based on the patient's medical history and contraindications to therapies. Surgical management should be considered for patients who are not clinically stable, are not suitable for medical management, or have failed to respond appropriately to medical management. The choice of surgical management should be based on the patient's underlying medical conditions, underlying pathology, and desire for future fertility. Once the acute bleeding episode has been controlled, transitioning the patient to long-term maintenance therapy is recommended.

Abnormal uterine bleeding (AUB) may be acute or chronic and is defined as bleeding from the uterine corpus that is abnormal in regularity, volume, frequency, or duration and occurs in the absence of pregnancy (1, 2). Acute AUB refers to 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 (1). Acute AUB may occur spontaneously or within the context of chronic AUB (abnormal uterine bleeding present for most of the previous 6 months). The general process for evaluating patients who present with acute AUB can be approached in three stages: 1) assessing rapidly the clinical picture to determine patient acuity, 2) determining most likely etiology of the bleeding, and 3) choosing the most appropriate treatment for the patient.

Assessment of the Patient With Acute Abnormal Uterine Bleeding

Initial evaluation of the patient with acute AUB should include a prompt assessment for signs of hypovolemia and potential hemodynamic instability. If the patient is hemodynamically unstable or has signs of hypovolemia, intravenous access with a single or two large bore intra-

venous lines should be initiated rapidly as should the preparation for blood transfusion and clotting factor replacements. After the initial assessment and stabilization, the next step is to evaluate for the most likely etiology of acute AUB so that the most appropriate and effective treatment strategy to control the bleeding can be chosen.

Etiologies of Acute Abnormal Uterine Bleeding

The etiologies of acute AUB, which can be multifactorial, are the same as the etiologies of chronic AUB. The Menstrual Disorders Working Group of the International Federation of Gynecology and Obstetrics proposed a classification system and standardized terminology for the etiologies of the symptoms of AUB, which has been approved by the International Federation of Gynecology and Obstetrics' executive board and supported by the American College of Obstetricians and Gynecologists (1, 2). With this system, the etiologies of AUB are classified as “related to uterine structural abnormalities” and “unrelated to uterine structural abnormalities” and categorized following the acronym PALM–COEIN: Polyp,

Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not otherwise classified (Fig. 1). Determining the most likely etiology of acute AUB is essential for choosing the most appropriate and effective management for the individual patient and is accomplished by obtaining a history, performing a physical examination, and requesting laboratory and imaging tests, when indicated.

History

Obtaining a thorough medical history should be guided by the PALM–COEIN system and focused on details of the current bleeding episode; related symptoms; and past menstrual, gynecologic, and medical history; which can, in turn, guide appropriate laboratory and radiologic testing. Up to 13% of women with heavy menstrual bleeding have some variant of von Willebrand disease and up to 20% of women may have an underlying coagulation disorder (2–4). Other coagulation factor deficiencies, hemophilia, and platelet function disorders may be associated with AUB in any age group. Using a screening tool in Box 1 can assist the clinician in determining which patients may benefit from laboratory testing for disorders of hemostasis. Additionally, systemic diseases, such as leukemia and liver failure, and medications, such as anticoagulants or chemotherapeutic agents, can impair coagulation and be associated with AUB.

Physical Examination

A physical examination of a patient who presents with acute AUB should focus on signs of acute blood loss

Box 1. Clinical Screening for an Underlying 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 the medical history. A positive screening result* comprises the following circumstances:

- Heavy menstrual bleeding since menarche
- One of the following conditions:
 - Postpartum hemorrhage
 - Surgery-related bleeding
 - Bleeding associated with dental work
- Two or more of the following conditions:
 - 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 screening result should be considered for further evaluation, including consultation with a hematologist and testing for von Willebrand factor and ristocetin cofactor.

Modified from Kouides PA, Conard J, Peyvandi F, Lukes A, Kadir R. Hemostasis and menstruation: appropriate investigation for underlying disorders of hemostasis in women with excessive menstrual bleeding. *Fertil Steril* 2005;84:1345–51. [PubMed] [Full Text]

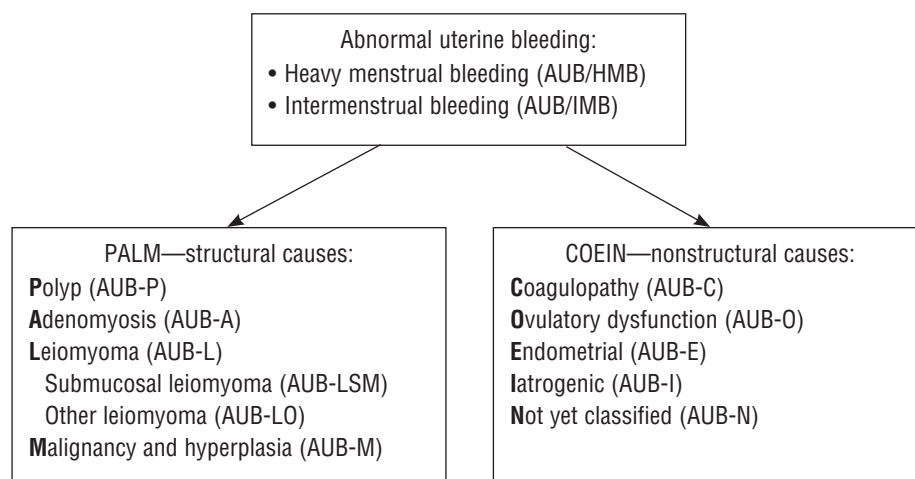


Fig. 1. Basic PALM–COEIN classification system for the causes of abnormal uterine bleeding in nonpregnant reproductive-aged women. This system, approved by the International Federation of Gynecology and Obstetrics, uses the term “abnormal uterine bleeding” paired with terms that describe associated bleeding patterns (“heavy menstrual bleeding” or “intermenstrual bleeding”), a qualifying letter (or letters) to indicate its etiology (or etiologies), or both. Abbreviation: AUB indicates abnormal uterine bleeding. (Data from Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO classification system [PALM–COEIN] for causes of abnormal uterine bleeding in nongravid women of reproductive age. FIGO Working Group on Menstrual Disorders. *Int J Gynaecol Obstet* 2011;113:3–13. [PubMed] [Full Text]) ⇄

(hypovolemia and anemia) and findings that suggest the etiology of the bleeding. The patient should be evaluated to determine that she has acute AUB and not bleeding from other areas of the genital tract. Thus, a pelvic examination (including a speculum examination and a bimanual examination) should be performed to identify any trauma to the genital tract and vaginal or cervical findings that could cause vaginal bleeding. The pelvic examination also will determine the amount and intensity of bleeding and will identify any uterine enlargement or irregularity, which can be associated with a structural cause of the acute AUB (leiomyoma).

Laboratory Testing and Imaging

Laboratory evaluation of patients who present with acute AUB is recommended (Table 1). All adolescents

and women with either abnormalities in initial laboratory testing or positive screening results for disorders of hemostasis should be considered for specific tests for von Willebrand disease and other coagulopathies, including von Willebrand–ristocetin cofactor activity, von Willebrand factor antigen, and factor VIII (2, 5). Based on the clinical presentation, a workup for thyroid disorders, liver disorder, sepsis, or leukemia may be indicated. Endometrial tissue sampling should be performed in patients with AUB who are older than 45 years as a first-line test. Endometrial sampling also should be performed in patients younger than 45 years with a history of unopposed estrogen exposure (such as seen in patients with obesity or polycystic ovary syndrome), failed medical management, and persistent AUB (2). In a stable patient, a decision whether to perform a pelvic ultrasound examination should be based on the clinical judgment of the examining clinician.

Table 1. Laboratory Testing for the Evaluation of Patients With Acute Abnormal Uterine Bleeding ↵

Laboratory Evaluation	Specific Laboratory Tests
Initial laboratory testing	<ul style="list-style-type: none"> Complete blood count Blood type and cross match Pregnancy test
Initial laboratory evaluation for disorders of hemostasis	<ul style="list-style-type: none"> Partial thromboplastin time Prothrombin time Activated partial thromboplastin time Fibrinogen
Initial testing for von Willebrand disease*	<ul style="list-style-type: none"> von Willebrand factor antigen[†] Ristocetin cofactor assay[†] Factor VIII[†]
Other laboratory tests to consider	<ul style="list-style-type: none"> Thyroid-stimulating hormone Serum iron, total iron binding capacity, and ferritin Liver function tests <i>Chlamydia trachomatis</i>

*Adult women who receive positive results for risk of bleeding disorders or who have abnormal initial laboratory test results for disorders of hemostasis should undergo testing for von Willebrand disease. Adolescents with heavy menses since menarche who present with acute abnormal uterine bleeding also should undergo testing for von Willebrand disease.

[†]Consultation with a hematologist can aid in interpreting these test results. If any of these markers are abnormally low, a hematologist should be consulted.

Data from James AH, Kouides PA, Abdul-Kadir R, Dietrich JE, Edlund M, Federici AB, et al. Evaluation and management of acute menorrhagia in women with and without underlying bleeding disorders: consensus from an international expert panel. *Eur J Obstet Gynecol Reprod Biol* 2011;158:124–34; National Heart, Lung, and Blood Institute. The diagnosis, evaluation, and management of von Willebrand disease. NIH Publication No. 08-5832. Bethesda (MD): NHLBI; 2007. Available at: <http://www.nhlbi.nih.gov/guidelines/vwd/vwd.pdf>. Retrieved December 5, 2012; and 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.

Treatment

Limited evidence and expert opinion support recommendations for treatment. Choice of treatment for acute AUB depends on clinical stability, overall acuity, suspected etiology of the bleeding, desire for future fertility, and underlying medical problems. The two main objectives of managing acute AUB are: 1) to control the current episode of heavy bleeding and 2) to reduce menstrual blood loss in subsequent cycles. Medical therapy is considered the preferred initial treatment (Table 2). However, certain situations may call for prompt surgical management (6). Studies of treatments of acute AUB are limited, and only one treatment (intravenous [IV] conjugated equine estrogen) is specifically approved by the U.S. Food and Drug Administration for the treatment of acute AUB.

Medical Management

Hormonal management is considered the first line of medical therapy for patients with acute AUB without known or suspected bleeding disorders. Treatment options include IV conjugated equine estrogen, combined oral contraceptives (OCs), and oral progestins. In one randomized controlled trial of 34 women, IV conjugated equine estrogen was shown to stop bleeding in 72% of participants within 8 hours of administration compared with 38% of participants treated with a placebo (7). Little data exist regarding the use of IV estrogen in patients with cardiovascular or thromboembolic risk factors.

Combined OCs and oral progestins, taken in multi-dose regimens, also are commonly used for acute AUB. One study compared participants who underwent therapy with OCs administered three times daily for 1 week with those who underwent therapy with medroxyprogesterone acetate administered three times daily for 1 week for the treatment of acute AUB (8). The study found that bleeding stopped in 88% of women who took OCs and 76% of women who took medroxyprogesterone acetate

Table 2. Medical Treatment Regimens ↔

Drug	Source	Suggested Dose	Dose Schedule	Potential Contraindications and Precautions According to FDA Labeling*
Conjugated equine estrogen	DeVore GR, Owens O, Kase N. Use of intravenous Premarin in the treatment of dysfunctional uterine bleeding—a double-blind randomized control study. <i>Obstet Gynecol</i> 1982;59:285–91.	25 mg IV	Every 4–6 hours for 24 hours	Contraindications include, but are not limited, to breast cancer, active or past venous thrombosis or arterial thromboembolic disease, and liver dysfunction or disease. The agent should be used with caution in patients with cardiovascular or thromboembolic risk factors.
Combined oral contraceptives [†]	Munro MG, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contraceptives for acute uterine bleeding: a randomized controlled trial. <i>Obstet Gynecol</i> 2006;108:924–9.	Monophasic combined oral contraceptive that contains 35 micrograms of ethinyl estradiol	Three times per day for 7 days	Contraindications include, but are not limited to, cigarette smoking (in women aged 35 years or older), hypertension, history of deep vein thrombosis or pulmonary embolism, known thromboembolic disorders, cerebrovascular disease, ischemic heart disease, migraine with aura, current or past breast cancer, severe liver disease, diabetes with vascular involvement, valvular heart disease with complications, and major surgery with prolonged immobilization.
Medroxyprogesterone acetate [‡]	Munro MG, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contraceptives for acute uterine bleeding: a randomized controlled trial. <i>Obstet Gynecol</i> 2006;108:924–9.	20 mg orally	Three times per day for 7 days	Contraindications include, but are not limited to, active or past deep vein thrombosis or pulmonary embolism, active or recent arterial thromboembolic disease, current or past breast cancer, and impaired liver function or liver disease.
Tranexamic acid	James AH, Kouides PA, Abdul-Kadir R, Dietrich JE, Edlund M, Federici AB, et al. Evaluation and management of acute menorrhagia in women with and without underlying bleeding disorders: consensus from an international expert panel. <i>Eur J Obstet Gynecol Reprod Biol</i> 2011;158:124–34.	1.3 g orally [§] or 10 mg/kg IV (maximum 600 mg/dose)	Three times per day for 5 days (every 8 hours)	Contraindications include, but are not limited to, acquired impaired color vision and current thrombotic or thromboembolic disease. The agent should be used with caution in patients with a history of thrombosis (because of uncertain thrombotic risks), and concomitant administration of combined oral contraceptives needs to be carefully considered.

Abbreviations: FDA indicates U.S. Food and Drug Administration; IV, intravenously.

*The U.S. Food and Drug Administration’s labeling contains exhaustive lists of contraindications for each of these therapies. In treating women with acute abnormal uterine bleeding, physicians often must weigh the relative risks of treatment against the risk of continued bleeding in the context of the patient’s medical history and risk factors. These decisions must be made on a case-by-case basis by the treating clinician.

[†]Other combined oral contraceptive formulations, dosages, and schedules also may be effective.

[‡]Other progestins (such as norethindrone acetate), dosages, and schedules also may be effective.

[§]Other dosages and schedules also may be effective.

within a median time of 3 days. For all patients, the contraindications to these therapies need to be considered before administration. Consultation with the Centers for Disease Control and Prevention's *Medical Eligibility Criteria for Contraceptive Use* (9, 10) and U.S. Food and Drug Administration labeling information (11) can be helpful in determining which patients may or may not be treated with OCs or progestin alone. Other OC and progestin formulations and dose schedules may be equally effective.

Antifibrinolytic drugs, such as tranexamic acid, work by preventing fibrin degradation and are effective treatments for patients with chronic AUB. They have been shown to reduce bleeding in these patients by 30–55% (12, 13). Tranexamic acid effectively reduces intraoperative bleeding and the need for transfusion in surgical patients and is likely effective for patients with acute AUB, although it has not been studied for this indication (14, 15). Experts recommend using either oral or IV tranexamic acid for the treatment of acute AUB (15). Intrauterine tamponade with a 26F Foley catheter infused with 30 mL of saline solution has been reported to control bleeding successfully and also may be considered (15, 16).

Once the acute episode of bleeding has been controlled, multiple treatment options are available for long-term treatment of chronic AUB. Effective medical therapies include the levonorgestrel intrauterine system, OCs (monthly or extended cycles), progestin therapy (oral or intramuscular), tranexamic acid, and nonsteroidal anti-inflammatory drugs (6). If a patient is receiving IV conjugated equine estrogen, the health care provider should add progestin or transition to OCs. Unopposed estrogen should not be used as long-term treatment for chronic AUB.

Patients with known or suspected bleeding disorders may respond to the hormonal and nonhormonal management options listed earlier in this section. Consultation with a hematologist is recommended for these patients, especially if bleeding is difficult to control or the gynecologist is unfamiliar with the other options for medical management. Desmopressin may help treat acute AUB in patients with von Willebrand disease if the patient is known to respond to that agent. It may be administered by intranasal inhalation, intravenously, or subcutaneously (17). This agent must be used with caution because of the risks of fluid retention and hyponatremia and should not be administered to patients with massive hemorrhage who are receiving IV fluid resuscitation because of issues with fluid overload (15). Recombinant factor VIII and von Willebrand factor also are available and may be required to control severe hemorrhage (5). Other factor deficiencies may need factor-specific replacement.

Patients with bleeding disorders or platelet function abnormalities should avoid nonsteroidal anti-inflammatory drugs because of their effect on platelet aggregation and their interaction with drugs that might affect liver function and the production of clotting factors (17).

Surgical Management

The need for surgical treatment is based on the clinical stability of the patient, the severity of bleeding, contraindications to medical management, the patient's lack of response to medical management, and the underlying medical condition of the patient. Surgical options include dilation and curettage (D&C), endometrial ablation, uterine artery embolization, and hysterectomy. The choice of surgical modality (eg, D&C versus hysterectomy) is based on the aforementioned factors plus the patient's desire for future fertility. Specific treatments, such as hysteroscopy with D&C, polypectomy, or myomectomy, may be required if structural abnormalities are suspected as the cause of acute AUB. Dilation and curettage alone (without hysteroscopy) is an inadequate tool for evaluation of uterine disorders and may provide only a temporary reduction in bleeding (cycles after the D&C will not be improved) (18). Dilation and curettage with concomitant hysteroscopy may be of value for those patients in whom intrauterine pathology is suspected or a tissue sample is desired (18). Case reports of uterine artery embolization and endometrial ablation show that these procedures successfully control acute AUB (19, 20). Endometrial ablation, although readily available in most centers, should be considered only if other treatments have been ineffective or are contraindicated, and it should be performed only when a woman does not have plans for future childbearing and when the possibility of endometrial or uterine cancer has been reliably ruled out as the cause of the acute AUB. Hysterectomy, the definitive treatment for controlling heavy bleeding, may be necessary for patients who do not respond to medical therapy.

Conclusions and Recommendations

Based on the available evidence and expert opinion, the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice makes the following conclusions and recommendations:

- The etiologies of acute AUB should be classified based on the PALM–COEIN system: **P**olyp, **A**domyosis, **L**eiomyoma, **M**alignancy and hyperplasia, **C**oagulopathy, **O**vulatory dysfunction, **E**ndometrial, **I**atrogenic, and **N**ot otherwise classified.
- Medical management should be the initial treatment for most patients, if clinically appropriate. Options include IV conjugated equine estrogen, multi-dose regimens of OCs or oral progestins, and tranexamic acid. Decisions should be based on the patient's medical history and contraindications to therapies.
- The need for surgical treatment is based on the clinical stability of the patient, the severity of bleeding, contraindications to medical management, the patient's lack of response to medical management, and the underlying medical condition of the patient. The choice of surgical modality should be based on

the aforementioned factors plus the patient's desire for future fertility.

- Once the acute bleeding episode has been controlled, transitioning the patient to long-term maintenance therapy is recommended.

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