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 Martinez-Perez j, Claire McIntock k, Flora Peyvandi l, Claire Philipp m, Jeffrey Wilkinson n, Rochelle Winikoff o

a Women’s Hemostasis and Thrombosis Clinic, Duke University Medical Center, Durham, NC, USA
b Department of Obstetrics and Gynecology, Royal Free Hospital, London, UK
c Division of Pediatric & Adolescent Gynecology, Department of Obstetrics & Gynecology, Baylor College of Medicine, Houston, TX, USA
d Department of Obstetrics and Gynecology, Danderyds University Hospital, Stockholm, Sweden
e Department of Hematology and Transfusion Medicine, Luigi Sacco University Hospital, Department of Internal Medicine, University of Milan, Milan, Italy
f Centre for Coagulation Disorders Rhine-Ruhr Area, Germany
i Emeritus Professor, University of London, London, UK
j Department Obstetrics and Gynecology, Fundacion Jimenez Diaz Hospital, Madrid, Spain
k Department of OB/GYN, National Women’s Health, Auckland City Hospital, Auckland, New Zealand
l Department for Diagnosis and Treatment of Coagulopathies, Angelo Bianchi Bonomi Hemophilia Thrombosis Centre, IRCCS Maggiore Policlinico Hospital, Mangiagalli and Regina Elena Foundation and Università di Milano, Milan, Italy
m Division of Hematology, Department of Medicine, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA
n Obstetrics and Gynecology, Minimally Invasive Gynecologic Surgery, Duke University Medical Center, Durham, NC, USA
o Hemosthia Treatment Center, CHU Sainte-Justine, Montreal, Quebec, Canada

ARTICLE INFO

Article history:
Received 5 October 2010
Received in revised form 25 February 2011
Accepted 30 April 2011

Keywords:
Acute menorrhagia
Bleeding disorder
Hemostasis management
Consensus
Coagulation factor

ABSTRACT

Acute menorrhagia is a common gynecological disorder. Prevalence is high among women with inherited bleeding disorders and recent guidance for optimal management is lacking. Following a comprehensive review of the literature, an international expert panel in obstetrics, gynecology and hematology reached consensus on recommendations regarding the management of acute menorrhagia in women without a diagnosed bleeding disorder, as well as in patients with von Willebrand disease, platelet function disorders and other rare hemostatic disorders. The causes and predictors of acute menorrhagia are discussed and special consideration is given for the treatment of women on anticoagulation therapy. This review and accompanying recommendations will provide guidance for healthcare practitioners in the emergency management of acute menorrhagia.

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⁎ Corresponding author. Tel.: +1 919 668 0011; fax: +1 919 681 7861.
E-mail address: james031@mcduke.edu (A.H. James).

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1. Introduction

Menorrhagia is a gynecological condition which adversely affects quality of life for many women. Acute menorrhagia can be defined as excessive menstrual or inter-menstrual bleeding occurring in a woman of childbearing age requiring emergency treatment excluding pregnancy, postpartum hemorrhage, trauma and malignancy [1,2]. Menorrhagia is usually defined by blood loss of over 80 ml per menstrual cycle, with anemia, low (below normal) ferritin levels, passing clots greater than a 50 pence-coin in size (1.1 in, or 2.8 cm in diameter) [3], and soaking of bed clothes or through a pad or tampon within 1 h [3,4] also being indicative of the condition. There are a variety of different causes of menorrhagia, and gynecological evaluation is essential to tailor management to the individual patient to prevent unnecessary invasive procedures which may have limited effect. Inherited bleeding disorders have been linked to a significant prevalence of menorrhagia [5], with von Willebrand disease (VWD), platelet function disorder and factor XI deficiency exhibiting a particularly high frequency [5,6]. The incidence and clinical significance of acute menorrhagia in women with underlying disorders of hemostasis, however, are often underestimated. Furthermore, the lack of recent evidence for diagnostic and treatment strategies in acute menorrhagia [7] necessitates the extrapolation from evidence in chronic menorrhagia. Guidelines for the evaluation and management of chronic menorrhagia in patients with an underlying disorder of hemostasis such as VWD were recently published following a consensus meeting of experts in hematology and obstetrics and gynecology [4]. To address the lack of guidance for the management of acute menorrhagia, a further meeting was held in November 2009 in London, UK, to reach consensus on the evaluation and management of acute menorrhagia particularly in the setting of an underlying disorder of hemostasis.

2. Methods

An extensive PubMed search was conducted to identify pertinent literature and evidence to guide the consensus. The terms ‘acute menorrhagia’, ‘menorrhagia and transfusion’ and ‘severe menorrhagia’ were entered with no restrictions placed on the dates of the search or the type of article, to ensure that all potential articles were identified. These terms were cross-referenced with von Willebrand disease, coagulation factor deficiency and platelet function defect.

Acute menorrhagia has not previously been rigorously defined. For the purpose of this consensus, the hematology and obstetric and gynecology experts defined acute menorrhagia as (1) life-threatening bleeding of uterine origin, (2) in the absence of pregnancy or malignancy, (3) occurring in women ranging from teen to perimenopausal age, (4) with or without previously diagnosed bleeding disorders, (5) presenting to the emergency department (ED), (6) with a need for immediate evaluation and treatment and (7) with potential need for both hemostatic and gynecological management.

2.1. Results of PubMed search

The PubMed search yielded case reports, small case series, review articles and guidelines, but no large observational studies. Randomized trials were found that addressed menorrhagia, but only one small randomized trial was found that addressed acute menorrhagia [8]. As a result, the recommendations provided in this consensus are based on the opinions of experts.

2.2. Causes and predictors of acute menorrhagia

There are a number of causes of acute menorrhagia, ranging from pathologies including systemic disease and coagulation disorders to anatomic conditions and treatment with some medications [9]. The causes of relevance to these guidelines, and the age groups which they affect, are shown in Fig. 1. Other causes that fall outside the present definition of acute menorrhagia include pregnancy-related complications and gynecologic malignancy.

The most likely causes of acute menorrhagia are in part determined by the age of the patient. Since the first clinical manifestation of menorrhagia is often related to the onset of menarche, underlying causes are seldom identified before adolescence [10]. Together with anovulatory bleeding, unidentified bleeding disorders are commonly associated with acute menorrhagia in this age range [9]. As the age of women increases, those suffering from acute menorrhagia with a history of underlying bleeding disorders may experience acute bleeding episodes due to continued sub-optimal management. Conversely, acute menorrhagia occurring as a result of local pathology such as fibroids or endometrial polyps is often not observed until women reach their mid-thirties [9]; perimenopausal anovulatory bleeding is usually not observed until women reach their mid to late forties [11].

2.3. Prevalence of hemostasis disorders in acute menorrhagia

VWD is one of the most common bleeding disorders associated with menorrhagia, with an overall prevalence of 13% in women presenting with chronic menorrhagia [6]. In turn, 74–92% of women with VWD experience menorrhagia, with the actual prevalence dependent on the VWD type [12–14]. Rare bleeding disorders are also associated with menorrhagia. A review of the literature on menorrhagia conducted in 2005 revealed a prevalence of 35–70% for women with deficiencies of factor I, XI or XIII [15]. Factors II, V and X have also been associated with a high prevalence of bleeding [16].
There are few prevalence studies of platelet disorders, including thrombocytopenic as well as thrombocytopenic disorders, in the setting of acute menorrhagia [17], and their prevalence may be underestimated. Studies of menorrhagia have identified a number of both inherited and acquired platelet disorders associated with the condition [18–22]. Based on the limited reports available, immune thrombocytopenic purpura (ITP) may be one of the most common causes of acute menorrhagia in adolescents [23]. As for

![Table 1](image)

**Table 1**

Evaluation of acute menorrhagia.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Adolescent (13–19 years)</th>
<th>20–35 years</th>
<th>35–50 years</th>
<th>Peri/postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anovulatory bleeding in the adolescent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding disorder (known or unknown)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic menorrhagia with acute deterioration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local pathology e.g. fibroid with necrosis or endometrial polyp</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adding of a new systemic disease e.g. leukaemia</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>Postoperative complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perimenopausal anovulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on relevant available literature [13, 28, 76, 77] and authors’ professional opinion/experience.

*Please note that VWF levels may not be altered by modern oral contraceptives [67].*
the prevalence of thrombocytopenic disorders in chronic menorrhagia, Philipp et al. reported that approximately half of patients presenting with unexplained menorrhagia had a defect in platelet aggregation and/or release [24,25].

2.4. Evaluation of acute menorrhagia

There was consensus that it is important to establish a diagnosis for and underlying cause of the abnormal bleeding, as this will help to ensure appropriate management of the bleeding and potentially prevent further bleeding. The experts also reached a consensus on how patients presenting with acute menorrhagia should be managed. The recommended evaluation is summarized in Table 1. The evaluation comprises a combination of patient history, including any family history (although lack of this should not exclude a diagnosis of an inherited disorder), ultrasound imaging, laboratory tests and spectum and pelvic examination. Depending on the accessibility of testing, the feasibility of achieving a meaningful specimen in the setting of acute menorrhagia and the ability to track the results from the ED, the provider may want to consider obtaining a Pap smear and endometrial biopsy at the time of examination. Otherwise, these tests can be postponed until the patient is stable and suitable follow-up provision is available. Testing of hormone levels, while potentially useful in the evaluation of continuing menorrhagia, is not essential in the evaluation of acute menorrhagia and can also be postponed. Due to the difficulties in obtaining some of the coagulation tests, there may be a tendency to withhold further evaluation; this can greatly impact on patient care. A number of studies and other consensus groups have highlighted the ongoing need to consider underlying bleeding disorders, especially in adolescents presenting with acute menorrhagia [4,5,9].

2.5. Optimal management strategies for acute menorrhagia in patients without a diagnosed bleeding disorder

Algorithms for the management of acute menorrhagia have been devised previously and these were considered during the development of this consensus [26]. A range of first-line treatment options was devised (Table 2); the order of use and whether they should be used alone or in combination is dependent on clinical judgment and social and cultural aspects. The options for first-line therapy include hormonal, surgical, and hemostatic treatments.

2.5.1. Hormonal treatment

The suggested regimens for the administration of hormonal preparations in acutely bleeding patients are detailed in Table 3. Once the patient has been stabilized, these regimens should be tapered to a maintenance dose. A variety of tapering regimens exist [27]; suggested regimens are summarized in Table 4.

2.5.2. Antifibrinolytic treatment

Tranexamic acid and aminocaproic acid are two commonly used antifibrinolytic agents. Although aminocaproic acid is still used in certain countries to treat acute bleeding, it has been largely replaced by tranexamic acid in countries where this is available. Therefore, the following discussion will focus principally on tranexamic acid. Tranexamic acid is used widely in the treatment and prophylaxis of mucous membrane and post-surgical bleeding; it is an effective first-line treatment for menorrhagia [28]. As a synthetic derivative of the amino acid lysine, tranexamic acid exerts its antifibrinolytic effect through the reversible blockade of lysine-binding sites on plasminogen molecules. Both intravenous (IV) and oral formulations are available, although the oral form is not currently available in some countries. The IV formulation has a

---

Table 2
Treatment options for acute menorrhagia in patients without a diagnosed bleeding disorder [8,70–77].

<table>
<thead>
<tr>
<th>First line</th>
<th>Second line (depending on the desire for future fertility)</th>
<th>Maintenance therapy (once stabilized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>antifibrinolytic agents</td>
<td>dilation and curettage (D &amp; C), which would be rarely indicated in adolescents, but this technique has value if a tissue sample is needed for diagnosis.</td>
<td>hormonal agents</td>
</tr>
<tr>
<td>hormonal agents (intravenous Premarin® [Pfizer Inc, New York, New York, USA] if available)</td>
<td>endometrial ablation, if no desire for future fertility</td>
<td>combined hormonal contraceptives</td>
</tr>
<tr>
<td>balloon tamponade</td>
<td>uterine artery embolization, if no desire for future fertility or as a life-saving measure</td>
<td>progestin only contraceptives including the levonorgestrel intrauterine device (Mirena® [Bayer Corporation, Leverkusen, Germany], injections (Depo-Provera® [Pfizer Inc, New York, New York, USA]) and the implanton® implant (Schering-Plough, Kenilworth, NJ, USA)</td>
</tr>
</tbody>
</table>

Table 3
Dose ranges of hormonal treatments in acute bleeding [27].

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Route</th>
<th>Protocol for acute menstural cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated oestrogens</td>
<td>IV</td>
<td>25 mg every 4-6h until bleeding stops, consider re-evaluating need for continuation at 48 h</td>
</tr>
<tr>
<td>30 μg ethinyl estradiol (or other 30 μg combination pill)</td>
<td>Oral</td>
<td>One tablet every 6 h until bleeding stops, consider re-evaluating at 48 h</td>
</tr>
<tr>
<td>50 μg ethinyl estradiol (or other 50 μg combination pill)</td>
<td>Oral</td>
<td>One tablet every 6 h until bleeding stops, consider re-evaluating at 48 h</td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>Oral</td>
<td>5–10 mg every 4 h</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>Oral</td>
<td>10 mg every 4 h (and up to 80 mg/day)</td>
</tr>
</tbody>
</table>

IV, intravenous.
faster onset of action and so may be more appropriate in some cases of acute menorrhagia. Tranexamic acid is contraindicated in patients with disseminated intravascular coagulation, venous or arterial thromboembolism, macroscopic hematuria or color blindness. Side-effects are uncommon but typically manifest as nausea and dizziness which respond to reductions in dose. While prolonged treatment may increase thrombotic tendency, large-scale studies have revealed that the incidence of thrombosis in women treated with tranexamic acid is similar to the spontaneous incidence of thrombosis in untreated women [29–31].

The usual IV dose of tranexamic acid is 10 mg/kg every 8 h and the usual oral dose is 20–25 mg/kg every 8 h. Various other dosing regimens are available for the oral formulation and these are listed in Table 5. No single dosing regimen has been demonstrated to be superior, although higher doses (3 g daily) may be more effective in acute menorrhagia than lower doses (2 g daily) [32]. In the United States, a new oral sustained formulation has recently been approved (dosed at two tablets of 650 mg each 1.3 g) orally three times per day [33]. (Neither this formulation nor this dose was studied in the treatment of acute menorrhagia.) Treatment duration is usually tailored according to clinical bleeding and may be stopped without tapering when heavy menstrual bleeding subsides.

2.5.3. Surgical treatment

When medical therapy fails in the treatment of acute menorrhagia, or if the patient has contraindications to medical management (i.e., thromboembolic disease), surgical management options must be considered. The choice of the surgical procedure is dictated by the suspected etiology and the desire for maintaining fertility after the procedure. Those procedures that can spare fertility include: dilatation and curettage (D & C), hysteroscopy with D & C, hysterectomy with polypectomy or myomectomy and endometrial balloon tamponade.

Endometrial balloon tamponade can be an effective means of controlling acute menorrhagia and allowing stabilization of the patient in anticipation of further medical (hemostatic, hormonal) therapy or other surgical procedures. In a uterus less than 12 weeks' size, a Foley catheter with a 30 cc balloon can be inserted through the cervix and inflated with saline until resistance of the myometrium is felt. Ultrasound can be helpful to diagnose intrauterine pathology, to confirm adequate placement and distension and to exclude ongoing bleeding above the balloon [34].

Uterine artery embolization (UAE) has been successful in the control of acute menorrhagia [35]. The aorta is accessed via the femoral artery, a pelvic angiogram is obtained, bleeding vessels are identified and then occluded [36]. The procedure entails inherent delay in transferring the patient to the angiography suite, preparing the patient and performing the procedure, and it must be regarded as second line therapy [36]. While successful pregnancies have been reported after this procedure [37], rates of pregnancy complications are increased after UAE and future fertility is still generally considered a contraindication to this procedure. Loss of ovarian function (transient or permanent) due to embolization of utero-ovarian collaterals can occur after UAE, leading to premature menopause. The risk of this complication is age-related and reported to be 1–2% in women younger than 45 years [28]; thus, this option should only be used as a life-saving measure in young women. Endometrial ablation has been demonstrated to be an effective means of controlling acute menorrhagia and has been proposed as an alternative to hysterectomy in women who are poor surgical candidates [38]. However, it still requires a minimum of local anesthesia or intravenous sedation, must be performed in the operating room or theater, should not be performed when malignancy has not been excluded and may not be successful in the presence of severe bleeding [39,40]. Pregnancy is contraindicated in women who have had endometrial ablation.

Hysterectomy is the most definitive surgical treatment of menorrhagia, but can often be avoided by employing one or more of the above measures. In a patient with acute, life-threatening hemorrhage, hysterectomy should not be delayed in favor of potentially less effective measures, especially if fertility is no longer desired or possible.

2.5.4. Multidisciplinary management

Multidisciplinary management of acute menorrhagia between gynecology, hematology, pharmacy and nursing staff can greatly benefit patient care. A sample care plan that ensures appropriate orchestration of these elements is presented in Fig. 2. This plan is in use at Sainte-Justine Hospital, Montréal, Canada, and has had a positive impact both on the success of controlling heavy bleeding and on improving the quality of care provided to women with acute menorrhagia [41]. It has also been associated with other benefits such as increased investigation for bleeding disorders, more consistent use of antifibrinolytic agents, fewer surgical interventions and fewer blood transfusions in adolescents presenting with acute menorrhagia. Such a care plan can be

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**Table 4**

Protocols for tapering hormonal treatment to maintenance therapy [27].

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Tapering regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 µg combination hormonal contraceptive pill</td>
<td>May begin with this every 6 h orally until bleeding stops, then decrease to every 8 h for 2 days and up to 7 days, then every 12 h for 2 days and up to 7 days, then daily thereafter. If transitioning from IV Premarin, may step down to 50 µg pill every 6 h or even every 8 h, then follow as above.</td>
</tr>
<tr>
<td>30–35 µg combination hormonal contraceptive pill Nor ethindrone acetate</td>
<td>May begin with this every 6 h orally until bleeding stops, then decrease to every 8 h for 2 days and up to 7 days, then every 12 h for 2 days and up to 7 days, then daily thereafter. 5–10 mg every 4 h orally until bleeding stops, then every 6 h for 4 days, then every 8 h for 3 days, then every 12 h for 2 days to 2 weeks, then daily thereafter. May switch over to this after initial bleeding stops if megestrol acetate utilised for acute menstrual control. 10 mg every 4 h orally (max 80 mg) until bleeding stops, then every 6 h for 4 days, then every 8 h for 3 days, then every 12 h for 2 days to 2 weeks, then daily thereafter. May switch over to this after initial bleeding stops if megestrol acetate utilised for acute menstrual control.</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td></td>
</tr>
</tbody>
</table>

IV, intravenous.

---

**Table 5**

Doses of tranexamic acid recommended for the treatment of acute menorrhagia.

- Tranexamic acid (500 mg tablets)
  - 500 mg four times daily
  - 1.0–1.5 g three times daily
  - 1 g every 6 h
  - 3 g over the day or one pill six times daily
  - 4 g daily for 3–5 days

- Tranexamic acid (650 mg tablets) [e.g., Lysteda™] [68]
  - 1.3 g three times daily for 5 days

modified to suit institutional requirements and should conform to usual care in that particular institution [42].

2.6. Management of acute menorrhagia in the patient with a hemostasis disorder

The general approach to the management of acute menorrhagia in the patient with a disorder of hemostasis is generally as described above with specifics as described below. Measures to control uterine bleeding should be implemented while correcting deficiencies of clotting factors or abnormalities of platelet number or function. The relative importance of hemostatic, hormonal and surgical treatment options will vary in each clinical situation. When bleeding is uncontrolled and other treatment options (hormonal therapy or antifibrinolytics) either have not yet been initiated or have not successfully elicited a reduction in bleeding, we recommend endometrial balloon tamponade with concomitant or subsequent hormonal and/or hemostatic therapy.

2.6.1. Management of acute menorrhagia in the patient with VWD

There are specific considerations for the first-line treatment of acute menorrhagia in patients with VWD which combine treatment options. Desmopressin must be used with caution, if

---

### Table 1: Sample care plan from the CHU Sainte-Justine, Montréal, Canada [42].

<table>
<thead>
<tr>
<th>Date and time of prescription</th>
<th>Time order taken</th>
<th>Time order faxed</th>
<th>Medical orders*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs q 30 minutes x 2, q 1 hour x 2, q 4 hours if stable, start pad and tampon count using pictorial blood loss assessment chart (PBAC), advise if pad changes more than 1 per hour are required, monitor in and out (fluid balance) q 4 hours, consultation with haematology.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV: Ringer’s lactate or normal saline. Rate: 120 cc/hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory tests:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before transfusion and/or hormone therapy draw the following tests (and keep a frozen plasma sample): complete blood count, coagulation studies (APTT, INR), fibrinogen, ferritin and VWD profile (VWF:Ag, VWF:RCoF, FVIII:C).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjugated oestrogens (e.g. Premarin®) first dose STAT: 2.5mg po qid or 25mg IV q 4–6 hours if patient does not tolerate po.</td>
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</tr>
<tr>
<td>Tranexamic acid (e.g. Cyklokapron®) first dose STAT: 25mg/kg (max 1500mg/dose) mg po tid or 10 mg/kg (max 600mg/dose) mg IV q 8 hours.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omit tranexamic acid if DIC, presence of venous or arterial thromboembolism, haemorrhage in closed space, presence of macroscopic haematuria or colour blindness. Should be used for the shortest duration required to control bleeding in women with known thrombophilia.</td>
<td></td>
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</tr>
<tr>
<td>Metoclopramide (e.g. Maxeran™) 0.1 mg/kg (max 10 mg) mg po q IV, 30–60 minutes before each dose of conjugated oestrogens, or promethazine 25–50mg po or IV 30–60 minutes before each dose of conjugated oestrogens if metoclopramide ineffective.</td>
<td></td>
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</tr>
<tr>
<td>Ondansetron (e.g. Zofran®) 0.15 mg/kg (max 8 mg) mg po or IV q 4 hours (maximum of 3 doses in 24 hours) 30–60 minutes before each dose of conjugated oestrogens.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>If Hb &lt;100g/L add: Ferrous sulfate 300mg po bid. Folic acid 5mg po qd.</td>
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</tbody>
</table>

*The dose of each prescribed medication is indicated in the appropriate section.

APTT, activated partial thromboplastin time; bid, twice daily; DIC, disseminated intravascular coagulation; Hb, haemoglobin; HR, heart rate; INR, international normalised ratio; IV, intravenous; po, orally; q, every; qid, qd, four times daily; STAT, immediately; tid, three times daily.

Fig. 2. Sample care plan from the CHU Sainte-Justine, Montréal, Canada [42].
at all, in cases of massive hemorrhage. Desmopressin causes fluid retention and patients receiving desmopressin should be fluid restricted, yet patients with acute menorrhagia commonly receive at least 1–2 L of fluid at the time of initial resuscitation. In the absence of massive hemorrhage, the recommendation for first-line treatment of acute menorrhagia in patients with VWD is desmopressin, which is frequently used in combination with an antifibrinolytic agent such as tranexamic acid (both for 2–3 days, then tranexamic acid alone for 3–4 days). This is based on a report that desmopressin and tranexamic acid together are more effective than either agent alone [43] with the presumption that acute menorrhagia is a clinical situation requiring as effective and rapid a response to hemostatic therapy as possible. Ideally, this approach should only be used in patients who have demonstrated a prior response to desmopressin (defined as a doubling of the VWF levels [14] and minimum VWF response of ≥50%) and in whom fluid overload would not be an issue. Factor concentrates (e.g., Haemate® P/Humate® P, CSL Behring, Marburg, Germany; Opti- vate®, Bio Products Laboratory, Elstree, UK; Alphanate®, Grifols UK Ltd., Cambridge, UK; and Wilate®, Octapharma, Lachen, Switzerland) are available [44] for VWF and FVIII replacement and these should be used if desmopressin is contraindicated; for example, in patients with no prior response (although if on-site real-time VWF analysis is available, one could conceivably measure post-desmopressin VWF levels 15 min post-infusion), in patients with potential for fluid overload, in patients with ongoing bleeding, in patients who are undergoing surgery [45] or in patients who are hemodynamically unstable. Maintenance therapy in patients with VWD should be the same as recommended above for patients without a diagnosed bleeding disorder. Intranasal or oral desmopressin, where available, could be added to augment this therapy [46].

2.6.2. Management of acute menorrhagia in the patient with thrombocytopenia or a platelet function disorder

Treatment for acute menorrhagia in patients with underlying thrombocytopenia or a platelet function disorder should include management of the underlying disorder. Platelet transfusion should be considered first-line therapy in patients with acute menorrhagia and a platelet count <20,000/μL or <50,000/μL with brisk bleeding, regardless of the etiology of thrombocytopenia. In patients with acute menorrhagia and thrombocytopenia undergoing procedures, platelet transfusion should be considered if the platelet count is <50,000 and for major surgery if the platelet count is <100,000.

2.6.3. Specific treatment for various thrombocytopenic conditions

In women with acute menorrhagia and ITP, specific treatment is indicated in addition to platelet transfusion. This should include intravenous immunoglobulin (IVIg) and initiation of corticosteroids [47]. For chemotherapy-induced complications, preventative therapy for subsequent cycles of chemotherapy may include gonadotropin-releasing hormone agonist maintenance to inhibit the menstrual cycle and reduce bleeding [48]. For patients with Glanzmann’s thrombasthenia, platelet transfusions are considered first-line treatment; however, if platelet transfusion refractoriness develops, then evidence suggests that recombinant factor VIIa (rFVIIa) is an alternative approach for cessation of bleeding [49]. Similarly, rFVIIa may be an effective second-line option in Bernard–Soulier disease [50]. Desmopressin may also be effective in Bernard–Soulier disease, Glanzmann’s thrombasthenia, and other platelet function disorders [51]. In cases of non-specific platelet function disorder (i.e., non-specific platelet aggregation and/or release abnormalities), desmopressin has been shown to shorten the bleeding time in approximately 50% of cases [51].

2.6.4. Management of acute menorrhagia in the patient with other rare bleeding disorders

Rare bleeding disorders should also be considered in patients presenting with acute menorrhagia, but any other contributing factors will need to be investigated. It is important to consider that cessation of menorrhagia in these patients may require more treatment in terms of specific replacement therapy of the deficient coagulation protein than for cessation of other types of bleeding.

Treatment should be as recommended for patients without a diagnosed bleeding disorder but will include specific factor replacement as necessary. Medical therapy should be regarded as the first choice of treatment as this may be the only option to preserve reproductive function. At present, there are limited data on prophylaxis of bleeding in these patients and on-demand treatment to stop bleeding is of utmost importance. Where possible, replacement should be achieved through the use of concentrated coagulation factors vis-à-vis the specific coagulation factor deficiency present. A number of single plasma-derived or recombinant coagulation factors are available as well as prothrombin complex concentrates (PCCs) which are concentrates of a number of coagulation factors, often containing three or four clotting factors and antithrombotic agents such as protein C and S (Tables 6 and 7) [52–54]. Due to the large volume of fresh frozen plasma (FFP) that is often required in massive hemorrhage (which may lead to fluid overload [52,55]) and due to the potential risk of transmitted infection, FFP should only be used to treat factor deficiency if no specific factor concentrate is available, for example, in factor V deficiency [56].

It should be noted that patients with fibrinogen deficiency, including afibrinogenemia and dysfibrinogenemia, are at an increased risk of thrombosis [57], and therefore hormonal therapy and antifibrinolytics should be used with caution until normal fibrinogen levels are restored. In fact, antifibrinolytics are contraindicated in the case of dysfibrinogenemia. In these patients, mechanical approaches such as balloon tamponade and contraceptive doses of a progestogen should be used before an estrogen or combined hormonal therapy is prescribed.

2.7. Management of acute menorrhagia in the patient on anticoagulation therapy

Despite the potential underlying risk of thrombosis in patients receiving anticoagulation therapy, it is universally accepted that reversal of anticoagulation should not be delayed in life-threatening bleeding [52,58,59]. There are several guidelines available which detail acceptable methods of anticoagulation reversal. In cases of life-threatening bleeding, these recommend that PCCs rather than FFP should be used in conjunction with

Table 6

<table>
<thead>
<tr>
<th>Factor</th>
<th>Brand</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>Clottagen®</td>
<td>LFB Benesia</td>
</tr>
<tr>
<td></td>
<td>Fibrinogen HT®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FIBROARA®</td>
<td>Shangai RAAS</td>
</tr>
<tr>
<td></td>
<td>Haemocomplettan P®/RiaSTAP®</td>
<td>CSL Behring</td>
</tr>
<tr>
<td>FVII</td>
<td>Facteur VII-LFB®</td>
<td>LFB Baxter BioScience</td>
</tr>
<tr>
<td></td>
<td>Factor VII</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td>FX</td>
<td>Factor X P Behring®</td>
<td>CSL Behring</td>
</tr>
<tr>
<td>FXI</td>
<td>Factor XI</td>
<td>BPL LFB</td>
</tr>
<tr>
<td>FXIII</td>
<td>Fibrogamin® P</td>
<td>CSL Behring</td>
</tr>
<tr>
<td></td>
<td>rFXIII-A2®</td>
<td>Novo Nordisk</td>
</tr>
</tbody>
</table>

* Currently on Phase 3 clinical trial as hemostatic agent.

Table 7
Constituents of commercially available prothrombin complex concentrates. Table reproduced from Levy et al. [54] with permission from the American Society of Anesthesiologists.

<table>
<thead>
<tr>
<th>Product (manufacturer): international availability</th>
<th>Factor content</th>
<th>Antithrombotic content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Protein C</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>VII</td>
</tr>
<tr>
<td></td>
<td>Label (U/ml)</td>
<td>Ratio (%)</td>
</tr>
<tr>
<td>Berjplex P/N (CSL Behring); major western European countries</td>
<td>20–48 133</td>
<td>10–25 69</td>
</tr>
<tr>
<td>Octaplex (Octapharma); major western European countries</td>
<td>11–36 98</td>
<td>9–24 66</td>
</tr>
<tr>
<td>Octaplex TIM 3 (Baxter); Italy, Austria</td>
<td>25 ≥15 100</td>
<td>Not in label</td>
</tr>
<tr>
<td>Prothromplex Total/S-TIM 4 Immuno (Baxter); Sweden, Germany, Austria</td>
<td>30 100</td>
<td>25 83</td>
</tr>
<tr>
<td>Prothromplex TIM 3 (Baxter); Italy, Austria</td>
<td>25 100</td>
<td>Not in label</td>
</tr>
<tr>
<td>Kaakadil (LFB); France</td>
<td>40 160</td>
<td>25 100</td>
</tr>
<tr>
<td>Uman Complex D.I. (Kedrion); Italy</td>
<td>25 100</td>
<td>Not in label</td>
</tr>
<tr>
<td>PPB-human SD/Nano (Octapharma); Germany</td>
<td>25–55 130</td>
<td>7.5–20 45</td>
</tr>
<tr>
<td>Profilnine (Grifola); USA</td>
<td>Present</td>
<td>Present (low)</td>
</tr>
<tr>
<td>Bebulin (Baxter); USA</td>
<td>Present</td>
<td>Present (low)</td>
</tr>
<tr>
<td>FEIBA (Baxter); USA</td>
<td>Present</td>
<td>Present (low)</td>
</tr>
</tbody>
</table>

Factor content ratios are based on the content of factor IX.
*In Europe, ranges are usually given on the product label, in accordance with the European Pharmacopoeia; single values are generally from older, national registrations.
PCC – prothrombin complex concentrate.
vitamin K administered either intravenously or orally [52,58,59]. In these patients, however, it is often sufficient to stabilize bleeding rather than achieve complete cessation, using the international normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT) as a guide. Mechanical approaches (e.g., balloon tamponade) are preferred over antifibrinolytics or hormones to stabilize the patient at risk of thrombosis, due to the increased risk of thrombosis with these agents.

In cases of severe menorrhagia, desmopressin [60] and/or platelet transfusion could be considered for patients on anti-platelet therapy [61]. In hemodynamically unstable patients receiving anti-platelet therapy, platelet transfusion should be considered primarily [62]. The threshold at which platelet transfusion would be considered for a patient on antiplatelet therapy is dependent upon the clinical scenario, but transfusion would certainly be considered during acute menorrhagia with a platelet count <50,000/μL. Although these treatments can help to improve bleeding, it is necessary to ensure that hemoglobin levels are restored in order to reconstitute platelet function.

Mechanical thromboprophylaxis is recommended in patients with a history of venous thromboembolism while the patient is not receiving anticoagulation [63]. An inferior vena cava filter should be considered in patients with a recent deep vein thrombosis or pulmonary embolism whose anticoagulation must be held or reversed [63]. Once the patient is stable, maintenance treatment will be as for patients not receiving anticoagulation; however, due to the increased risk of thrombosis in these patients, estrogen and antifibrinolytics are contraindicated. Furthermore, once the patient is stable, full anticoagulation should be resumed, bridging with intravenous unfractionated heparin or subcutaneous low molecular weight heparin [58].

3. Future perspectives

Owing to the lack of available data on acute menorrhagia, further studies are required to fully assess the epidemiology, risk factors and treatments for acute menorrhagia. Many of the recommendations for treatment are based on studies in chronic menorrhagia, which may not be entirely indicative of the acute condition. Epidemiological studies could generate prevalence data on patients who present to the ED, require admission to hospital, or otherwise require emergency treatment for acute menorrhagia (all causes). Furthermore, prospective studies could, and should, be designed to provide data on the risk factors for bleeding, e.g., to examine whether low hemoglobin levels trigger bleeding (by decreasing platelet aggregation, as red cells function as a 'scaffold' for platelet aggregation) and whether uremia is a risk factor for bleeding. These could also help to elucidate the contribution of multiple factors as causes of bleeding. While it would be ideal to validate the suggested treatment protocols, treatment research is difficult to undertake due to the ethical considerations for randomized controlled trials in the acute setting; in this case, extrapolation from studies in chronic menorrhagia may be more appropriate. Comparison of management protocols used in a large numbers of institutions could, however, provide valuable insights into treatment outcomes.

4. Conclusions

Optimizing the management of acute menorrhagia remains of clinical importance due to the life-threatening nature of the condition. The wide variety of causes of the condition emphasize the need to correctly evaluate the underlying causes and tailor management accordingly. Future studies will help to further elucidate treatment options.

Disclosure of interest

Dr. Andra James has received research support, honoraria and served on Advisory Committees for CSL Behring and has received honoraria from Grifols.

Dr. Peter Kouides has received research support and honoraria from CSL Behring; he has served on Advisory Committees for CSL Behring, Novo Nordisk, Baxter and Bayer and has acted as a Consultant for Xanodyne Pharmaceuticals.

Dr. Rezan Abdul-Kadir has received honoraria from CSL Behring. Dr. Jennifer E. Dietrich has received honoraria from CSL Behring and Merck. She has served as a Consultant for CSL Behring and has received research funding from Duramed Pharmaceuticals.

Dr. Mans Edlund has received honoraria from CSL Behring, research support from Ferring and has acted as a Consultant for Xanodyne Pharmaceuticals.

Dr. Augusto B. Federici has served on the Advisory Committees of Baxter, CSL Behring, Grifols and Octapharma and received honoraria from Baxter, CSL Behring, Grifols, Kedrion and Octapharma.

Dr. Susan Halimeh has received honoraria from CSL Behring. Dr. Pieter Willem Kamphuisen is a consultant for CSL Behring and has received research grants from Wyeth, Bayer and Novo Nordisk.

Dr. Martinez-Perez has received honoraria for CSL Behring.

Dr. Lee has been the chairperson for two DSBMs for Novo Nordisk and is a founding editor of the journal Haemophilia published by Wiley Blackwell. She received travelling and hotel expenses from CSL Behring.

Dr. Claire McIntock has received honoraria and served on Advisory Committees for CSL Behring and Novo Nordisk and has acted as a Consultant for Novo Nordisk.

Dr. Flora Peyvandi has received honoraria from Novo Nordisk and CSL Behring.

Dr. Claire Philipp has received research support and honoraria and served on advisory committee for CSL Behring.

Dr. Jeffrey Wilkinson has received honoraria from CSL Behring. Dr. Rochelle Winikoff has received honoraria and served on Advisory Committees for CSL Behring.

Contribution to authorship

All authors attended and presented at a consensus meeting held on 16–17 November 2009. All authors provided presentations that were used as the basis of this consensus and fully contributed to the discussions during the meeting and in the development of the manuscript.

Funding

Financial support for the consensus meeting and paper was provided by CSL Behring (Marburg, Germany).

Acknowledgements

Editorial support for this paper was provided by Fishawack Communications.

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