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Cover Picture

James Lind: Conqueror of Scurvy

Surgeon of Britain's Royal Navy abroad H.M.S Salisbury, in the English Channel in 1747, James Lind Conducted a series of clinical experiments that definitely proved citrus fruits or their juices would cure scurvy, dread dietary-deficiency disease that killed a million seamen between 1600 and 1800. Dr. Lind's work, at sea, in Edinburgh, and at Haslar Naval Hospital, plus his three books, on scurvy, on care of sailors' health, and on tropical diseases, had much to do with reforming naval health practices, saving lives both on sea and land, and shaping destinies of nations, as world commerce increase.

The Sri Lanka Prescriber

Advances in the Management of Upper Gastrointestinal Bleeding: A Review

Abstract

Upper gastrointestinal bleeding (UGIB) is a frequent medical emergency, presenting with a variety of symptoms, including melena, hematemesis, hematochezia, coffee-ground vomiting, and sometimes anemia. Peptic ulcer disease is the most common cause of UGIB, followed by variceal bleeding and other less frequent etiologies. Initial clinical assessment in suspected UGIB focuses on stabilizing the patient and identifying the underlying cause. After resuscitation, prompt and systematic medical management and endoscopic evaluation should follow to establish a diagnosis and initiate definitive care. In most cases, combined medical and endoscopic therapy is effective, and advanced radiological interventions or surgery may be required in select cases.

Key words: Upper gastrointestinal bleeding, variceal bleeding, peptic ulcer disease, endoscopy

Introduction

Upper gastrointestinal bleeding (UGIB) is a serious and common medical condition, often leading to frequent hospital admissions. UGIB is defined as bleeding that originates above the ligament of Treitz, affecting the esophagus, stomach, or duodenum [1]. The main causes of UGIB include peptic ulcer disease (PUD), erosive esophagitis/gastritis, variceal bleeding, upper gastrointestinal cancers, and several other less common causes. Patients with UGIB typically present with hematemesis, melena, coffee-ground vomit, and occasionally hematochezia. Some cases, however, may have more subtle presentations, such as symptoms of anemia due to ongoing occult bleeding or positive fecal occult blood tests.

Timely assessment and stabilization are essential for hemodynamically unstable patients. Effective management involves identifying the source of bleeding (site and etiology), assessing severity, developing a treatment plan based on endoscopic findings, and arranging for appropriate long term follow up.

Epidemiology

The incidence of UGIB shows considerable variability worldwide. Although the incidence of UGIB has been decreasing, the hospital admissions and mortality rates associated with UGIB remain significantly high [2].

Etiology and pathophysiology

Worldwide, peptic ulcer disease (PUD) is the leading cause of upper gastrointestinal bleeding (UGIB), followed by variceal bleeding. Causes of UGIB are broadly categorized into variceal and non-variceal bleeding, allowing for treatment approaches tailored to the specific underlying pathology. Table 1 outlines both common and less common causes of UGIB.

Table 1: Causes of Upper Gastrointestinal Bleeding

Non-variceal UGIB		Variceal UGIB
Esophagus	Gastro-esophageal reflux disease (GORD) Esophageal malignancy Pill esophagitis Erosive esophagitis Infectious esophagitis Mallory-Weiss tear	Esophageal varices Gastric varices Duodenal varices
Stomach	Erosions Peptic ulcer disease (PUD) Gastric malignancy Portal hypertension gastropathy Gastric antral vascular ectasia (GAVE) Dieulafoy's lesions	
Duodenum	Ulcers/ Erosions Diverticulum Haemosuccus pancreaticus Duodenal malignancy – Adeno carcinoma/ Periampullary carcinoma/ Lymphoma	

PUD is defined as an ulcer in the stomach or duodenum that extends through the muscularis mucosa into the submucosa or muscularis propria. The main causes of PUD include *Helicobacter pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs), both of which disrupt the protective lining of the stomach and duodenum. Less common causes include Curling ulcer, Cushing ulcer and autoimmune gastritis.

Variceal bleeding is seen in cirrhosis with portal hypertension or with portal vein thrombosis. Acute variceal bleeding occurs in approximately 25-50% of patients with cirrhosis and carries a substantial mortality, affecting up to a third of these patients [3].

Clinical presentations and diagnosis

Commonly expected findings in the history and examination of patients with UGIB are summarized in Table 2.

Table 2: Common clinical presentations of Upper Gastrointestinal Bleeding patients

History	
Site of bleeding	Oral, nasal, esophagus and stomach or lungs
Severity of bleeding	Hematemesis, melena / associated hematochezia
Timing of bleeding	Acute vs chronic
Complication	Features of anaemia (palpitation, fatigue, chest pain)
Aetiology	Variceal Bleeding: History of liver disease/ chronic alcohol use Drug history: NSAIDS, antiplatelets, anticoagulants Malignancy: Loss of appetite and loss of weight GORD: Reflux symptoms and epigastric pain Mallory-Weiss tear: Severe retching and profound vomiting Curling ulcer/Cushing ulcer: critically ill, burn, intracranial pathology
Examination	
Initial assessment (Vitals)	Airway, Breathing (SPO2), circulation (pulse, BP, CRFT),disability (GCS)
Aetiology	Evidence of liver disease: Jaundice, oedema, flaps, peripheral stigmata of cirrhosis (palmer erythema, gynecomastia, spider naevi etc.) Evidence of chronic alcohol use: Parotid enlargement, Dupuytren's contracture etc. Features of malignancy: Virchow's node, axillary node (late) Abdominal examination: Hepatomegaly, splenomegaly, abdominal tenderness / mass
Complication	Pallor

NSAIDS: Non-steroidal anti-inflammatory drugs, GCS: Galscow coma scale, CRFT: Capillary refilling time, BP: Blood pressure

Initial management and risk stratification

The initial clinical assessment may give a clue regarding the potential cause of the UGIB; however, a definitive diagnosis requires direct visualization with esophago-gastro-duodenoscopy (OGD). Regardless of etiology, all patients presenting with UGIB should undergo systematic resuscitation and stabilization of their vital organs.

Airway management is critical, as there is a risk of aspiration. Ensuring the airway patency and considering intubation and ventilation, where necessary, especially if endoscopy is planned in a patient with low GCS (<8/15) [4]. Supplemental oxygen via nasal cannula may be beneficial in certain cases. Patients should be kept nil by mouth. Insertion of nasogastric tube has its advantages and disadvantages: It can be used to decompress the stomach, identify internal bleeding early and feeding when appropriate. On the contrary it can induce bleeding from esophageal varices by continuous irritation and erosion of varices.

Signs of significant blood loss include tachycardia (heart rate >100 bpm), hypotension (systolic blood pressure <90 mmHg), tachypnoea, delayed capillary refill time (>2 seconds), and reduced urine output.

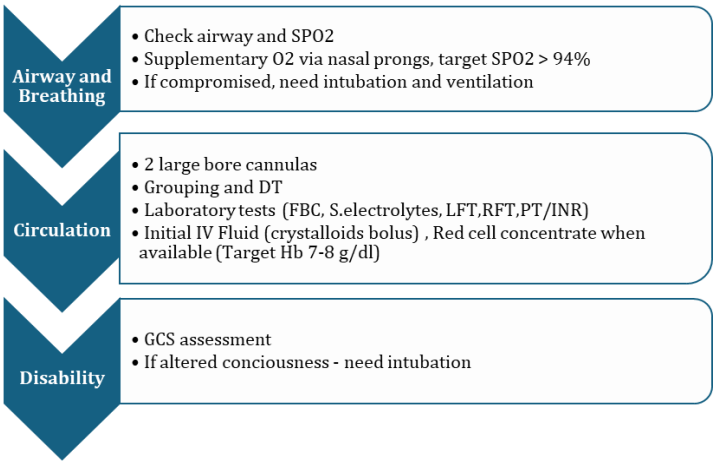
Two large-bore (14G or 16G) peripheral IV cannulas should ideally be placed in the antecubital fossae to provide rapid infusion. If peripheral access is challenging, central venous access or intraosseous access may be used. One cannula should be used for blood collection for crossmatching and laboratory testing (including complete blood count, serum electrolytes, PT/INR, liver function, and renal function tests), while the other is used for fluid resuscitation.

In acute bleeding, initial hemoglobin (Hb) levels may not immediately reflect the severity of hemorrhage due to the time required for the actual drop and hemoconcentration. Therefore, serial Hb monitoring is more useful than a single value. Transfusions with packed red blood cells should be used conservatively, targeting a hemoglobin level between 7-8 g/dl. The transfusion policy in individual patients should also consider other factors such as cardiovascular disorders (target Hb 9-10g.dl), age, hemodynamic status and ongoing bleeding. In acute variceal bleeding, transfusion of fresh frozen plasma is not recommended as it will not correct coagulopathy and may lead to volume overload and worsening of portal hypertension. Also, it is important to note the there is no evidence that platelet count and fibrinogen levels are correlated with the risk of failure to control bleeding or rebleeding. However, if bleeding is not controlled, correction of the hemostatic abnormalities should be considered on a case-by-case basis [5].

Crystalloid fluids are recommended for initial resuscitation until blood products become available. Over-resuscitation should be avoided as it may worsen bleeding, and goal-directed fluid therapy is preferred. Figure 1 describes the summary of initial resuscitation.

Several scoring systems are available for risk assessment and prognostication in patients with UGIB. These include pre-endoscopic scoring tools, such as the pre-endoscopy Rockall score, AIMS65, and the Glasgow Blatchford score, as well as post-endoscopic tools like the full Rockall score. The Rockall score is particularly valuable, as it is widely used to predict mortality and the risk of re-bleeding in patients with variceal or ulcer-related bleeding [6].

Figure 1: Summary of initial resuscitation



Definitive management

Following initial stabilization and comprehensive clinical evaluation, management should proceed with a structured approach tailored to the suspected etiology. We can divide this into three phases: pre-endoscopic management, endoscopic assessment and intervention, and post-endoscopic care. Current guidelines recommend performing early endoscopy within 12-24 hours in cases of UGIB depending on the clinical status of the patient: Urgent overnight endoscopy should only be requested for hemodynamically unstable patients [*7*].

Pre endoscopic management

Most guidelines recommend stopping anti-thrombotics on admission in patients with acute UGIB especially if given for primary cardiovascular prevention. For secondary prevention, guidelines are less clear; however, in cases of severe bleeding, anti-thrombotics may be temporarily withheld and drugs like aspirin may be resumed within 3-5 days based on the patient's clinical status [8]. Evidence is limited when managing dual antiplatelet therapy during UGIB, and decisions should consider individual patient factors and cardiology input. In non-severe UGIB, aspirin should generally be

continued, while P2Y12 inhibitors can be withheld and recommenced within five days.

Guidelines recommend withholding anticoagulants, such as warfarin, in cases of major UGIB, with reversal measures including four-factor prothrombin complex, fresh frozen plasma, or vitamin K. For minor bleeding, the decision to hold anticoagulation should weigh the risks and benefits. Re-initiation of anticoagulation remains a subject of debate but should be done as soon as possible when indicated for thrombo prophylaxis [8].

In cases of UGIB, NSAIDs should be discontinued. Prokinetic agents, such as erythromycin and metoclopramide may improve visualization during endoscopy and reduce the need for repeat procedures [9].

The use of antifibrinolytic agents, like tranexamic acid, is generally not recommended; randomized trials have not shown benefit in UGIB, and there is an associated risk of thrombosis [8,9]. Some studies suggest that pre-endoscopic intravenous proton pump inhibitors (PPIs) in severe UGIB may reduce the need for endoscopic intervention, administered either as an infusion or in intermittent doses, with comparable efficacy. After endoscopy if variceal bleeding is found as the reason for the UGIB, PPIs should be stooped. However, European, Asian-Pacific, International, and U.S. guidelines vary in their recommendations on pre-endoscopic PPI use.

1. **Pre endoscopic management for variceal bleeding**

Esophageal and gastric variceal bleeding require combined pharmacological and endoscopic treatment. Bacterial infections are common in cirrhotic patients with variceal bleeding; therefore, empirical treatment with third-generation intravenous cephalosporins or oral ciprofloxacin is recommended to reduce mortality and rebleeding risk [8]. Vasopressors such as terlipressin, octreotide, and vasopressin should also be initiated and continued for 48 to 72 hours to decrease portal pressure and control bleeding, with all three showing similar efficacy. Terlipressin is contraindicated in patients with cardiac or severe vascular disease. Beta blockers should be withheld during acute UGIB in cirrhotic patients as it may interfere with haemodynamic monitoring.

2. **Pre endoscopic management for non-variceal bleeding**

In addition to initial resuscitation and discontinuation of antiplatelets, anticoagulants, and NSAIDs, intravenous proton pump inhibitors (PPIs) should be promptly administered as an 80 mg bolus followed by either continuous infusion or intermittent twice daily dosing for 48 hours. Testing for Helicobacter pylori during the acute setting may lead to false negative results. Therefore, testing and eradication should be undertaken after 4 weeks to reduce the risk of ulcer recurrence and rebleeding.

Endoscopic management

In UGIB, esophagogastroduodenoscopy serves both diagnostic and therapeutic roles. Endoscopy should ideally be performed within 24 hours of admission, or within 12 hours in severe cases. Globally, peptic ulcers are the most common finding on OGD, and the Forrest classification is widely utilized to categorize ulcer morphology, severity, and guide treatment.

Endoscopic treatment options for ulcers include adrenaline injection (1:10,000), which must be combined with either thermal coagulation, argon plasma coagulation, or mechanical methods such as haemoclips. Adrenaline alone provides only temporary haemostasis and should not be used as a stand alone therapy and must be paired with one of the additional techniques [8].

For esophageal variceal bleeding, endoscopic band ligation is recommended, while gastric varices are managed with cyanoacrylate glue injection. Gastric varices, though less common, carry a poorer prognosis compared to esophageal varices. New treatment options like Endoscopic ultrasound (EUS) guided coiling and glue injection of the feeder vessels of the varices have shown to be more effective and can be used where facilities are available.

Rebleeding is a potential complication following endoscopy. In cases of rebleeding, repeat endoscopy

is indicated, and further interventions such as angioembolization with interventional radiology or surgical intervention may be required. Balloon tamponade using a Sengstaken-Blakemore tube can serve as a temporary measure to control uncontrolled variceal bleeding until endoscopy can be performed but is rarely used in practice now.

A transjugular intrahepatic portosystemic shunt (TIPS) may be used to reduce portal pressure in patients who have not responded to medical and repeated endoscopic therapies. However, TIPS does not confer a survival benefit and is associated with an increased risk of hepatic encephalopathy in cirrhotic patients [10]. For patients with gastric varices who have clinical or anatomical contraindications to TIPS, balloon-occluded retrograde transvenous obliteration (BRTO) is an alternative with comparable efficacy [8].

Post endoscopic management

After endoscopic treatment, patients with non-variceal bleeding should continue oral PPI therapy for an additional 8-12 weeks. Severe cases require higher doses, while mild cases can be managed with standard twice-daily doses, which significantly reduces the risk of rebleeding.

For variceal bleeders, vasoactive medications should be continued for 2-5 days post-endoscopy, antibiotics for 7 days, and PPI therapy for 2 weeks. Once the acute bleeding episode has resolved, nonselective beta blockers may be reintroduced for secondary prophylaxis. For this indication carvedilol is considered better than propranolol. Regular endoscopic surveillance, initially at 2-4 weeks and thereafter at 6-12 months is recommended to monitor progress and assess need for reintervention. Figure 2 summarizes the management of acute UGIB.

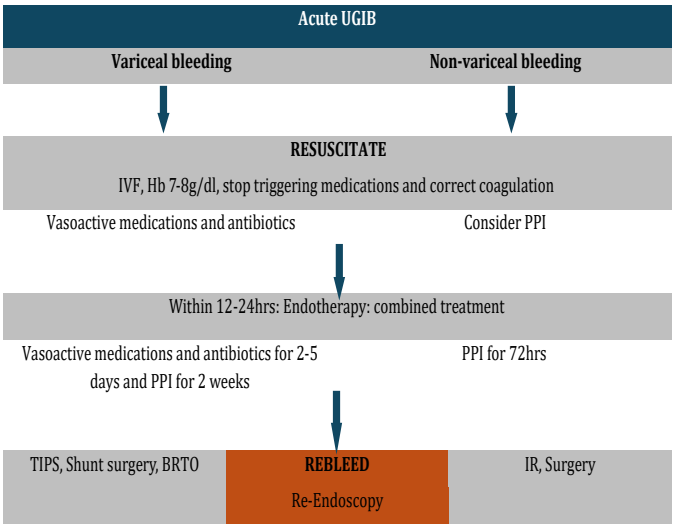


Figure 2: Summary of management of acute upper gastrointestinal bleeding (UGIB) management

IVF: Intravenous fluids, Hb: Haemoglobin, PPI: Proton-pump inhibitor, TIPS: Transjugular intrahepatic portosystemic shunt, BRTO: Balloon-occluded retrograde transvenous obliteration

Conclusion

Upper gastrointestinal bleeding (UGIB) remains a condition with considerable morbidity and mortality. Effective management centers on prompt stabilization, comprehensive clinical evaluation, risk stratification, and timely medical and endoscopic intervention. These steps resolve most UGIB cases, while advanced interventions and surgical options are reserved for patients who do not respond to initial treatments.

Competing interests

The authors declare that they have no competing interests

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Management of menopause

SUMMARY

During perimenopause and after menopause, women may experience diverse symptoms. All women require a comprehensive assessment of their current health and risks for future disease, appropriate screening, and promotion of a healthy lifestyle. Menopausal hormone therapy is the most effective treatment for menopausal symptoms. It can be offered to symptomatic patients with no contraindications following an individualised discussion about the risk of harms versus benefits. Menopausal hormone therapy is recommended for women with premature ovarian insufficiency (menopause occurring before 40 years of age) regardless of symptoms, unless contraindicated. Nonhormonal medications may improve symptoms for women who have contraindications to, or do not wish to take, menopausal hormone therapy.

Keywords
estrogen, menopausal hormone therapy, perimenopause, progestogen, tibolone

(Aust Prescr 2023;46:48–53)

Introduction

The average age of menopause in Australian women is 51 years. Perimenopause typically lasts several years before menopause, during which fluctuating ovarian function and hormone concentrations affect the menstrual cycle.1 Box 1 lists definitions related to menopause. Menopause can occur spontaneously, be induced by medical treatments (e.g. chemotherapy, radiotherapy) or by surgical removal of the ovaries. Approximately 75% of women experience symptoms during perimenopause and after menopause, with 25% experiencing moderate to severe symptoms affecting their quality of life.3 Multiple symptoms typically occur (see Box 2), including vasomotor symptoms (e.g. hot flushes, night sweats), joint and muscle pains, mood changes, sleep disturbance, low libido and genitourinary symptoms. Menopause is also associated with an increased risk of osteoporosis and cardiovascular disease.4

Box 1 Definitions related to menopause

menopause—the final menstrual period or the permanent cessation of ovarian function

early menopause—menopause occurring at 40 to 44 years of age

premature ovarian insufficiency—menopause occurring before 40 years of age; women may experience oligomenorrhoea and amenorrhoea during this time[2]

perimenopause—from when the menstrual cycle starts changing until 12 months after menopause

postmenopause—from 12 months after menopause

In this article, the term ‘women’ only refers to cisgender women. Trans- and gender-diverse people may also experience menopausal symptoms and may benefit from appropriately tailored health services.

Management for menopausal symptoms

The management of menopausal symptoms (see Box 2) includes an assessment of the patient’s: • general health, current symptoms and concerns

- risks of cardiovascular disease and osteoporosis
- need for screening and preventive activities.

During perimenopause, a menstrual bleeding history should be documented, noting any abnormal bleeding that requires investigation, before considering systemic menopausal hormone therapy (MHT).

Box 2 Common perimenopausal or menopausal symptoms

- menstrual cycle changes in length (longer or shorter) and flow (heavier or lighter)
- vasomotor symptoms (hot flushes, night sweats)
- mood changes
- cognitive concerns ('brain fog')
- sleep disturbance
- musculoskeletal symptoms
- low libido
- formication (sensation of insects crawling under the skin)
- genitourinary symptoms (vaginal dryness, dyspareunia, urinary urgency, urinary frequency, recurrent urinary tract infections)

Depending on individual symptoms, management may include nonpharmacological and pharmacological (including hormonal and nonhormonal) therapies, which are discussed below.

Any ongoing need for contraception should be determined.5

Premature ovarian insufficiency (see Box 1) can be associated with increased health risks to women. Women with premature ovarian insufficiency require comprehensive assessment and management. MHT is recommended regardless of symptoms (unless contraindicated) until the usual age of menopause, to reduce the risks of osteoporosis and cardiovascular disease.6

MHT is the most effective treatment for menopausal symptoms.4 It can be offered to symptomatic patients with no contraindications following individualised discussions about risk of harms versus benefits and other therapies available.

Other established benefits of MHT include improved quality of life, and prevention of osteoporosis and, potentially, cardiovascular disease.4,7,8 Estrogen therapy is suitable for the management of osteoporosis or low bone density in women younger than 60 years of age.9

Useful resources to assist practitioners in assessing and managing menopause include:

• A Practitioner's Toolkit for the Management of the Menopause from the Women's Health Research Program at Monash University
• Menopause health professional tool from Jean Hailes for Women's Health.

Nonpharmacological treatments for menopausal symptoms

Lifestyle modifications such as exercise, weight loss and reducing alcohol consumption may be helpful for some women. These measures may not reduce the severity of symptoms but may make them more manageable and improve overall wellbeing. Cognitive behavioural therapy can reduce the impact of vasomotor symptoms and alleviate sleep disturbance.10,11

Menopausal hormone therapy for menopausal symptoms

Menopausal hormone therapy (MHT) is indicated for treatment of menopausal symptoms. It is highly effective for alleviating vasomotor symptoms and may improve sleep disturbance, mood changes, cognitive concerns and musculoskeletal symptoms.4.
Regimens used for MHT include:
• estrogen-only for women who have had a total hysterectomy; unopposed estrogen is associated with endometrial hyperplasia and potential malignancy
• combined estrogen plus progestogen for women with a uterus:
– cyclic combined MHT—continuous estrogen with a progestogen given cyclically (e.g. for 12 to 14 continuous days of a calendar month)
– continuous combined MHT—continuous estrogen and progestogen
• tibolone for women more than one year after menopause, particularly those with low libido.

Women starting on MHT must be warned about adverse effects, including nausea and breast tenderness. Women should be reviewed after 6 to 12 weeks of starting MHT to evaluate ongoing menopausal symptoms and any adverse effects. At this review, dosage or formulation adjustments can

be made; for example, if vasomotor symptoms remain problematic, the estrogen dose can be increased. Annual reassessment is recommended to ensure health screening is up to date and to review the need for ongoing treatment.

Women prescribed cyclic MHT should expect a regular vaginal bleed at the end of the progestogen phase. Some women may have irregular bleeding and spotting when starting cyclic MHT, and adjusting therapy can help (e.g. increasing the progestogen dose or duration). For both cyclic and continuous combined regimens, bleeding and spotting often settles over months, but if it persists beyond 6 months, or becomes heavy or prolonged, it should be investigated.

There is no maximal duration of MHT defined. Many women wish to stop MHT after some time to assess whether their symptoms still warrant treatment. Some may elect to continue MHT indefinitely. This latter group must be counselled about the potential long- term harms of MHT (see below).

For a complete list of MHT formulations available in Australia, refer to the Guide to MHT/HRT doses from the Australasian Menopause Society.

Estrogen

Estrogen is the primary component of MHT. Most formulations contain either estradiol or conjugated equine estrogens.12 Estradiol is preferred because it is structurally similar to 17-beta-estradiol, the commonest naturally occurring estrogen in premenopausal women. Various estradiol preparations are available (e.g. oral tablets or capsules, transdermal patch or gel). Systemic estrogen should be started at a low-to-medium dose and adjusted according to symptoms.

Estrogen is effective for treating genitourinary symptoms (e.g. vaginal dryness, urinary frequency, recurrent urinary tract infections).13 Genitourinary symptoms often improve in women taking systemic MHT, but some require additional topical vaginal estrogen.

Topical vaginal estrogen is only appropriate for managing genitourinary symptoms. Low-dose vaginal estrogen (estradiol or estriol)12 is available as vaginal tablets, pessaries or creams and does not require the addition of a progestogen.

Progestogens and combination preparations

Progestogens are required for women with a uterus who are prescribed estrogen-containing MHT.

For perimenopausal women, cyclic MHT is used, where a progestogen is given cyclically with estrogen (e.g. for 12 to 14 continuous days of a calendar month). For postmenopausal women, continuous combined MHT is used, where a progestogen is given continuously with estrogen.

If continuous combined MHT is used by perimenopausal women, irregular bleeding frequently occurs; cyclic MHT is recommended to minimize irregular bleeding. Once a woman has been using cyclic MHT for 12 months, a trial of continuous combined MHT can take place.

Several progestogens are available for use in MHT (e.g. micronised progesterone, dydrogesterone, drospirenone, norethisterone, medroxyprogesterone acetate). Their properties vary—for example, some are more androgenic while others exert anti-mineralocorticoid effects. No randomised controlled trial data are available to guide choice.14 Micronised progesterone and dydrogesterone (which is structurally similar to natural progesterone) may have a lower breast cancer risk than older synthetic progestogens15 and, for most women, are considered first line.

Most progestogens are given orally as tablets or capsules, either in a fixed-dose combination product with estrogen, or as separate preparations. Transdermal patches contain a combination of

estradiol and norethisterone. A progestogen-releasing intrauterine device (IUD), the 52 mg levonorgestrel-releasing IUD, can be used for up to 5 years in combination with estrogen. It has the added benefit of providing contraception and managing heavy menstrual bleeding.

Women younger than 50 years of age, without contraindications, can use combined hormonal contraception such as a combined oral contraceptive pill for MHT. This has the benefit of providing symptomatic relief, menstrual-cycle control, and contraception.

Tibolone

Tibolone is a synthetic steroid that is metabolised into components with estrogenic, progestogenic and androgenic actions. It is useful for postmenopausal women, particularly those with low libido. The usual dose is 2.5 mg orally, daily.

Clinical trials have demonstrated low-dose tibolone (e.g. 1.25 mg orally, daily) may reduce both vertebral and nonvertebral fractures. It can also be used to treat low bone density.16

Tibolone should only be prescribed to women who are more than one year after menopause as it can cause vaginal bleeding. Women with a history of breast cancer should not be prescribed tibolone. Tibolone is associated with increased risk of stroke in women older than 60 years of age.16

Cardiovascular disease risk and MHT

Menopause is also associated with an increased risk of cardiovascular disease.4
Women who start MHT younger than 60 years of age, or within 10 years of menopause, have reduced all-cause mortality and risk of coronary heart disease. These women also have fewer cardiac events on long-term follow up.17 These findings support the 'timing hypothesis',18 where women who start MHT close to menopause experience a cardiovascular benefit, whereas those who start MHT several years after menopause do not experience this benefit.19 At present there is no role for MHT in the primary prevention of cardiovascular disease; however, in women with premature ovarian insufficiency, MHT may reduce the risk of cardiovascular disease and should be used until the usual age of menopause.

Contraindications to MHT

Strong contraindications to MHT include, undiagnosedvaginal bleeding, and a history of breast or endometrial cancers, or acute cardiovascular or thromboembolic events. Other contraindications to prescribing MHT are listed in Box 3.
Transdermal estrogen (rather than oral) may be recommended for women with:
• a history of atherosclerotic heart disease or stroke
• a history of migraine with aura
• treated cardiovascular disease risk factors (e.g. hypertension, dyslipidaemia)
• increased risk of venous thromboembolism
• hepatobiliary disease.

Box 3 Precautions for menopausal hormone therapy (MHT)

Contraindications to MHT

- hormone-dependent cancers including breast and endometrial [NB1]
- undiagnosed vaginal bleeding
- acute cardiovascular event
- acute venous thromboembolism [NB2]
- porphyria cutanea tarda
- severe liver disease

Conditions where caution is recommended with MHT

- past myocardial infarction, transient ischaemic attack or stroke [NB3] [NB4]
- high risk of venous thromboembolism [NB3]
- active liver disease [NB3]
- migraine with aura [NB3]
- hypertriglyceridaemia [NB3]
- hepatobiliary disease [NB3]
- high risk of breast cancer
- age older than 65 years and no prior use of MHT

NB1: MHT is generally safe to use in patients with treated stage 1 endometrial malignancy.
NB2: Consider transdermal estrogen for MHT if the patient is anticoagulated.
NB3: Exercise caution with oral estrogen; transdermal estrogen is preferred for MHT.
NB4: Treated hypertension is not a contraindication to MHT use.
Adapted from reference 20.

Risk of harms associated with MHT

For most women younger than 60 years, or within 10 years of menopause, the risks of MHT are low and outweighed by the benefits.4 Estrogen-only MHT is associated with endometrial hyperplasia and potential malignancy due to unopposed estrogenic effects, and therefore use is limited to women who

have had a total hysterectomy. For conditions where caution is recommended when prescribing MHT, see Box 3.20

Breast cancer

The Women's Health Initiative trials found the combination preparation of conjugated equine estrogens+medroxyprogesterone acetate was associated with an increased incidence of breast cancer.8 Women taking conjugated equine estrogens alone had a reduced risk of breast cancer,21 highlighting the role of progestogens. The risk of breast cancer has been linked to the duration of MHT.14 Observational data suggest that micronised progesterone and dydrogesterone may confer a lower risk of breast cancer than older synthetic progestogens.15

Thromboembolic disease

Oral estrogen undergoes first-pass metabolism in the liver and alters the hepatic production of coagulation factors. This is associated with a 2- to 3-fold increase in venous thromboembolism, but the absolute risk remains low. Estradiol and estetrol theoretically have lower risks of venous thromboembolism, though strong evidence for this is lacking. Transdermal estrogen does not carry this risk and is the preferred option for women with risk factors for venous thromboembolism or cardiovascular disease.22,23

Nonhormonal drugs and other preparations for menopausal symptoms

Table 1 lists typical doses of nonhormonal drugs used for vasomotor symptoms of menopause. Nonhormonal drugs may be useful for women with contraindications to MHT (see Box 3) or who do not wish to take MHT. Generally, nonhormonal drugs are less effective than MHT and do not confer the bone- or cardiovascular-protective benefits of estrogen. Most of the drugs have limited use because of their adverse effects.10

Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) have modest effects on vasomotor symptoms and may improve sleep and mood.

Gabapentin and oxybutynin may reduce the frequency and severity of vasomotor symptoms. The North American Menopause Society no longer recommends clonidine or pregabalin for treatment of vasomotor symptoms because of their adverse effects; however, they are still used in some instances in Australia.10

Unlike vasomotor symptoms, genitourinary symptoms do not improve with time. Nonhormonal lubricants can be helpful for vaginal dryness.

Complementary therapies and herbal preparations (e.g. black cohosh, phytoestrogens) have insufficient evidence of benefit, can cause adverse effects, and are not recommended.20,24 Custom-compounded, bioidentical hormone therapy is also not recommended because of limited dose regulation and lack of safety data.4

Emerging treatments

Emerging options for the treatment of menopausal symptoms include estetrol, an estrogen found in the fetal liver, and neurokinin 3 receptor antagonists.20 Estetrol may provide some safety advantages through reduced effects on liver and breast tissue.25 Neurokinin 3 receptor antagonists are promising nonhormonal treatments for vasomotor symptoms.20,26 A 2023 randomised placebo-controlled trial reported the neurokinin 3 receptor antagonist, fezolinetant, was effective and well tolerated for the treatment of vasomotor symptoms.27

Table 1 Nonhormonal drugs for vasomotor symptoms

Drug [NB1]	Dosage	Adverse effects
serotonin and noradrenaline reuptake inhibitors		
desvenlafaxine	25 to 150 mg orally daily	dizziness, nausea, sexual dysfunction
venlafaxine	37.5 to 150 mg orally daily	
selective serotonin reuptake inhibitors		
citalopram	10 to 20 mg orally daily	dizziness, nausea, sexual dysfunction
escitalopram	5 to 20 mg orally daily	
paroxetine [NB2]	10 to 25 mg orally daily	
other drugs		
clonidine [NB3]	25 to 75 micrograms orally twice daily	dizziness, drowsiness, constipation
gabapentin	100 to 900 mg orally daily in up to 3 divided doses	drowsiness, dizziness, possible withdrawal symptoms
oxybutynin [NB4]	2.5 to 5 mg orally twice daily	dry mouth, drowsiness, blurred vision

NB1: All drugs listed in the table, except clonidine, are not registered by the Therapeutic Goods Administration for treating vasomotor symptoms.

NB2: Paroxetine should not be co-administered with tamoxifen; co-administration can cause inhibition of cytochrome P450 2D6 and reduce the efficacy of tamoxifen.

NB3: Clonidine may be used but is no longer recommended because of its adverse effects.[10]

NB4: Oxybutynin may help symptoms of overactive bladder; however, it may cause adverse effects, particularly cognitive decline in older people.[10]

Conclusion

MHT is highly effective for the relief of symptoms associated with menopause. For most women within 10 years of menopause or younger than 60 years of age, the benefits are likely to outweigh the risk of harms. The benefits of MHT are not only limited to symptom control, but also good evidence supports its role in prevention of osteoporosis and cardiovascular disease. Local vaginal preparations can be used for genitourinary symptoms only. Women should be counselled on their therapeutic options and prescribed a regimen tailored to their individual needs.

Conflicts of interest

Karen Magraith has received honoraria for presentations from Mylan, Jean Hailes for Women's Health, and the Australasian Menopause Society.

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