Bleeding, Hemorrhagic Shock, and the Global Blood Supply

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KEYWORDS

• Hemorrhage • Hemorrhagic shock • Blood transfusion • Global health • Critical care

KEY POINTS

- Bleeding is responsible for high mortality and morbidity worldwide, and safe blood is a scarce resource, especially in low- and middle-income countries.
- Timely recognition and addressing the "lethal diamond" – coagulopathy, hypothermia, acidosis, and hypocalcemia – is key to better outcomes in treating hemorrhagic shock.- Traumatic injury, obstetric hemorrhage, and upper gastrointestinal bleed are the leading causes of severe bleeding requiring transfusion.
- While hemorrhagic shock requires urgent blood for transfusion, a 114 million unit shortfall makes transfusion scarce or impossible in much of the world. Blood scarcity is a complex, multifactorial issue in low-resource environments encompassing donor supply, availability, and management; processing and testing of blood; and administration and post-transfusion monitoring.

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INTRODUCTION

Hemorrhage is responsible for at least 40% of deaths after trauma and 27% of maternal deaths worldwide.[1,2] Patients with hemorrhagic shock are among the most acutely ill that are treated in medicine; attentive critical care and transfusion of blood products are requisites to avoid death resulting from acidosis, coagulopathy, hypothermia, hypocalcemia, and multisystem organ failure. And although the availability of safe blood for transfusion is central to the management of severe bleeding, safe blood is a scarce resource, especially in low- and middle-income countries (LMICs).[3] In this review, the authors provide a brief overview of bleeding, hemorrhage, and hemorrhagic shock; describe its epidemiology as well as the key diagnostic and management approaches to the major causes of hemorrhagic shock in the global context; and provide an overview of the current barriers to transfusion and emerging solutions in many of the world's poorest areas.

Definitions

Bleeding is the loss of blood components from the cardiovascular system. There are several types of bleeding, ranging from location, rate, and duration. The Oxford dictionary defines hemorrhage as "severe loss of blood from a damaged blood vessel inside a person's body."[4] What precisely separates bleeding from hemorrhage is less defined, but brisk bleeding is known as hemorrhage. And when hemorrhage progresses unchecked, it leads to inadequate oxygen delivery for cellular metabolism and thereby tissue hypoxia; this state is known as hemorrhagic shock. **Table 1** provides detailed definitions for various classifications of bleeding.

Recognizing Hemorrhagic Shock

Although unchecked hemorrhage can quickly progress to hemorrhagic shock and death within a matter of minutes, the initial signs of hemorrhagic shock can be subtle and may not show until the patient has lost an extensive amount of blood. **Table 2** outlines the widely accepted classes of hemorrhagic shock, which are based on the traditional classifications based on volume of blood lost.[5] Newer studies suggest that the rate of blood loss is as important a factor as the total blood loss.[6]

Nonetheless, alterations in mental status or increases in respiratory rate, slight agitation, or increased anxiety might be some of the only signs of early hemorrhagic shock in otherwise young and healthy patients. Pale, ashy, or cyanotic skin and a capillary refill time more than 2 seconds can be direct evidence of inadequate tissue perfusion.[7] A fast central pulse and a weak or absent peripheral pulse suggest hypotension. The Advanced Trauma Life Support manual has famously taught that the presence of a peripheral pulse suggests a systolic blood pressure (SBP) of at least 80 mm Hg, and a central pulse typically correlates with an SBP of 60 mm Hg.[5] There is some debate as to the exact blood pressures required to generate a palpable pulse, but the radial pulse will disappear before a femoral pulse that will disappear before a carotid pulse.[8] Hence, as the carotid pulse is often the easiest location to palpate a central pulse, its presence should not lower concern for severe hemorrhagic shock although its absence does correlate strongly with severe hemorrhagic shock. Finally, hypotension itself may be a late finding in healthy young adults, and the provider should not rule out severe bleeding in the setting of normal blood pressure.

Pathophysiology of Hemorrhagic Shock and the Lethal Triad

A complex combination of processes on the cellular and tissue level leads to the well-known "lethal triad" of coagulopathy, hypothermia, and acidosis in severe

Table 1
Types of bleeding by blood components and duration

Type of Bleeding	
By location of bleeding:	
Internal	Happens when blood leaked from blood vessels is contained within the body, usually in a cavity.
External	Happens when blood leaked from blood vessels exits through an open injury in the skin.
By type of blood:	
Capillary	Very slow blood loss. Most common, the least dangerous, easy to control by applying pressure.
Venous	Flowing, darker red blood (lower O2). Steady but not as strong as arterial flow.
Arterial	Pulsatile, bright red blood (more O2). Usually from lacerations, punctures, amputations. Arterial blood is lost at an increased speed compared with others, so it is usually the most dangerous.
By frequency:	
Acute	Happens when there is abrupt blood loss in a short time span, which results in reduction of circulating blood. Sharp circulating volume loss causes immediate body responses to compensate for new hypoxic state.
Chronic	Happens due to a gradual and continuing blood loss over a longer period of time. Usually, circulating blood volume is maintained. In the early stages, patients present with mild iron deficiency anemia, and the body compensates for the blood loss.
Acute-on-chronic	Acute transformation of a chronic condition managed as acute. Usually occurs in overlap with acute bleeding (eg, hematemesis or chronic GI bleeding). This is usually seen in patients with portal hypertensive lesions.

Table 2
Classification of hemorrhage by severity

Class	
Class I (Mild)	Blood volume loss of up to 15% with heart rate minimally elevated or normal but no change in BP, pulse pressure, and respiratory rate
Class II (Moderate)	Blood volume loss between 15% and 30% with HR (100–120), RR,[20–24] decreased pulse pressure with a normal or minimally changed systolic blood pressure. Skin may be cool to touch, and moist, capillary refill may be delayed.
Class III (Severe)	Blood volume loss between 30% and 40%, significant decreases in blood pressure $\pm$ mental status changes. SBP < 90 and drop in BP >20%–30% from presentation are of particular concern. Assume this is due to bleeding until proved otherwise. Heart rate $\geq$ 120 and "thready" with elevated RR and decreased urine output.
Class IV (Severe)	Blood volume loss >40%, significant decreases in blood pressure $\pm$ mental status changes. Hypotensive (SBP < 90), narrowed pulse pressure ($\leq$25 mm Hg), and HR > 120. Skin will be cold and pale, and capillary refill will be delayed.

Data from American College of Surgeons. Committee on Trauma. Advanced Trauma Life Support: Student Course Manual (Tenth Edition). American College of Surgeons; 2018.

hemorrhagic shock and worsens outcomes.[9] Because blood delivers oxygen to tissues, hemorrhage leads to diminished oxygen delivery. The resulting transition to anaerobic metabolism leads to an accumulation of lactic acid, free radicals, and other inflammatory molecules.

Concomitantly, although the coagulation cascade activates at the local site of blood loss to promote fibrin formation, blood clotting, and limiting blood loss, systemic inflammatory markers activate endothelium in other parts of the body into a fibrinolytic state.[10] In states of injury and bleeding, this is a protective physiologic response that allows for a prothrombotic state at the site of injury while protecting against unnecessary clot formation in other regions of the body. In severe hemorrhage, this typically careful balance between local fibrin formation and systemic fibrinolysis is dysregulated, and a profound coagulopathy ensues.

Finally, to complete the triad, blood loss results in massive dissipation of heat. With lower body temperatures comes diminished function of critical enzymes, including those central to the clotting cascade; this further potentiates blood loss and the triad of coagulopathy, acidemia, and even more hypothermia.

There is increasing consensus that the "lethal triad" should be modified into the "lethal diamond" to account for the important role of calcium in this process and prompt providers to take note (**Fig. 1**).[11] Calcium plays a central role in the coagulation cascade, its presence is essential for cardiac contractility and vascular tone, and hypothermia can worsen hypocalcemia by affecting the hepatic processing of citrate. Further, necessary transfusion can exacerbate hypocalcemia, perpetuating the cycle.

On a more macro level, severe hypovolemia from hemorrhage leads to decreased perfusion of critical body tissues, leading to multisystem organ failure. In the most extreme, irreversible circumstance, reduced perfusion of the brain and heart leads to death from brain anoxia and nonperfusing cardiac arrhythmias. In less severe but often equally debilitating circumstances, multisystem organ failure ensues from hypoperfusion of the kidneys, liver, intestine, and extremities.

The Key Role of Critical Care: Rewarming and Appropriate Resuscitation

The role of high-quality critical care in the treatment of hemorrhagic shock is obvious. High-quality warming is central to addressing the lethal diamond. Forced air and convection warming devices are highly effective in maintaining an appropriate patient temperature and ubiquitous in the high-income country setting.[12] Many different techniques exist, some better than others, including the use of warming blankets and warmed fluids, and techniques can be tailored to the local context.[13]

Although appropriate resuscitation is essential to breaking the deadly downward spiral of hemorrhagic shock, inappropriate resuscitation can potentiate it. Remarkably, for decades, crystalloid administration was the first step in the resuscitation of hemorrhage-related hypovolemia. The adverse impact of this approach on severe hemorrhage has only been fully recognized over the past decade: (1) crystalloid temporarily enhances circulating volume at the expense of diluting blood's oxygen-carrying capacity, clotting factors, and platelets, worsening blood loss and coagulopathy; (2) cold, acidic crystalloid solutions further bicarbonate losses and lower body temperature, furthering acidemia- and hypothermia-related enzyme dysfunction; and (3) crystalloid solution is only transiently retained in the intravascular space, worsening interstitial edema in multiple body organs and compartments.[14]

Similar to replacement of lost blood volume with crystalloid, replacement with packed red blood cells (PRBC) alone is also inadequate. A PRBC resuscitation strategy, although improved over crystalloid, also can potentiate coagulopathy instead of breaking the cycle.[15] As over a decade of evidence has now shown, resuscitation with

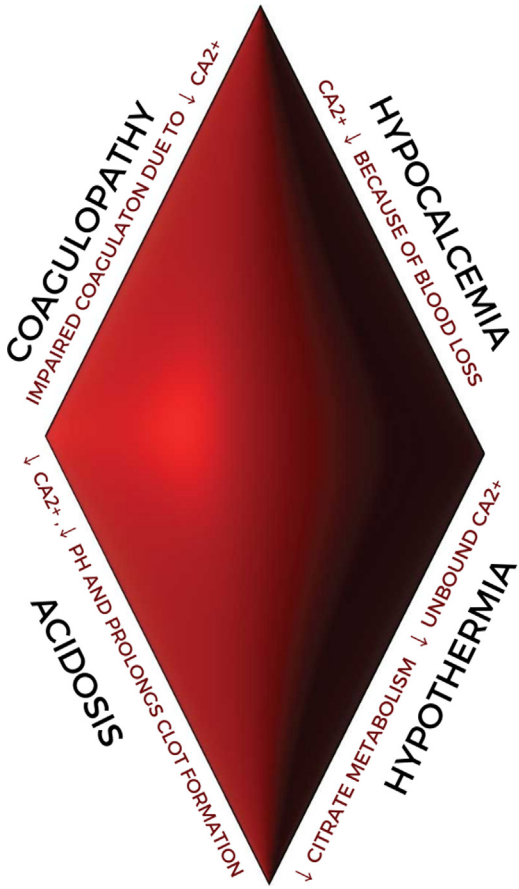

Fig. 1. The "lethal diamond." Ca2+ represent calcium ions.

blood products must be carefully "balanced," replacing all the components of blood that are lost with severe hemorrhage.

Evidence-backed consensus now supports an equal ratio of platelets and plasma relative to blood products administered during resuscitation or a target ratio of 1:1:1.[16] Even though science is evolving, whole blood is likely the preferred transfusion fluid for severe hemorrhagic shock. Although a 1:1:1 ratio of PRBC to plasma and platelets approximates the composition of whole blood, it does not achieve it.[17] Whole blood has a higher concentration of red blood cells, platelets, and clotting factors compared with its 1:1:1 approximation.

HEMORRHAGE IN TRAUMA

Epidemiology

Trauma is one of the 10 leading causes of death and disability in the world and is the lead cause of death for the young.[18,19] Accidental injury constitutes the highest proportion of global injury burden, responsible for more than 5 million deaths per year, almost equal to 9% of global annual mortality.[20] Road traffic injury itself kills 1.3 million and injures 50 million annually.[21] Ninety percent of these deaths occur in LMICs, and

the risk of death in a road traffic collision is more than 3 times higher in LMICs than in high-income countries (HICs).[21] Violence and self-inflicted injuries account for 16% of injury-related mortality worldwide but are the leading cause of death among 15- to 44-year-olds.[22]

In the context of this massive global injury burden, its notable that up to 29% of all injury-related deaths are considered preventable, and uncontrolled bleeding accounts for 64% of these preventable deaths.[23] And although most of the hemorrhage-related deaths (56%) occur before arrival to definitive care,[24] hemorrhage accounts for the largest proportion of mortality within the first hour in emergency services care. Half of hospital deaths within the first 24 hours and 80% of operating room deaths after major trauma are due to bleeding.[24]

Initial Evaluation

As famously stated by the "Advanced Trauma Life Support" program, the top 3 causes for hypotension in trauma are "bleeding, bleeding, and bleeding."[5]

Two quick calculations can help serve as decision aids and either raise or lower the clinician's suspicion for bleeding: (1) the Shock Index and (2) the Assessment of Blood Consumption (ABC) Score. The Shock Index is simply a ratio of the patient's heart rate to the SBP.[25] A ratio of less than 0.7 is considered typically normal, but ratios at 0.9 and higher should elicit concern for hemorrhage.

The ABC score was designed to predict the need for a massive blood transfusion and consists of 4 easy-to-calculate components: tachycardia, hypotension, presence of penetrating trauma mechanism, and a bedside ultrasound positive for intrabdominal free fluid. Presence of 2 or more of these is considered a high likelihood of requiring a transfusion.[26]

Diagnosis

The "primary" and "secondary" surveys are focused evaluations incorporating physical examination, vital signs, and bedside imaging to identify emergent physiologic and anatomic threats to life. Identifying bleeding is a core objective.

External bleeding can lead to blood loss in the field before hospital arrival and, although usually easy to identify, can be hidden by hair, clothing, and in areas not immediately obvious to the examiner. As such, manual palpation and visual exploration of every surface—palpating the scalp underneath hair, turning patients on their side to visualize the back—are key elements of the initial evaluation to identify external bleeding.

Hemodynamically significant internal bleeding can occur in almost any closed body cavity and can be less obvious. Identifying where the patient is bleeding is critical, as it will guide management. The chest, abdomen, pelvis, and extremities can harbor significant quantities of blood. Bleeding in the abdomen is approached very differently than bleeding in the extremity, chest, or pelvis. Assessing for chest trauma, "softness" of the abdomen, and extremity compartments and checking the pelvis for stability are important to raise the examiner's suspicion for potential hemorrhage at these sites. The thigh compartment, for example—especially in the obese with lots of soft tissue—can easily harbor more than a liter of blood.

Imaging adjuncts are often necessary to diagnose or rule out internal bleeding. The extended Focused Assessment for Sonography in Trauma is a bedside ultrasound examination that can be performed as part of the trauma evaluation. It works to identify free fluid in the abdominal, chest, and pericardial spaces. Although a negative FAST examination does not rule out bleeding, a positive one is highly predictive. FAST can have lower sensitivity (68%) in patients with blunt abdominal injury, and a

reference test such as computed tomography (CT) should be performed next. On the other hand, the FAST specificity is very high (95%) for the presence of internal hemorrhage.[27] The hazard ratio increases by 1.5 for every 10 minutes increase in time to the operating room after a positive FAST examination.[28] Chest and pelvis radiographs can help quickly assess whether there is fluid in the chest or pelvic fracture, respectively, allowing the clinician to either adjust their level of concern for bleeding in these areas. CT scan is often the next line of imaging but does not have a role in management of patients with severe hemorrhage and hemodynamic instability. Surgery should not be delayed if there is an indication of emergent laparotomy, as patients with bleeding can rapidly decompensate while obtaining diagnostic imaging and are typically in a setting (the radiology suite) that makes them less accessible for immediate intervention, if needed. Similarly, the CT imaging should not be performed if it delays transferring the patient to another center for definitive care.[5]

Management

Rapid bleeding should be addressed with rapid urgency. External hemorrhage should be controlled on initial evaluation. High-quality compression should be to areas that can be compressed (the scalp, most parts of the skin). When this is inadequate in the extremities, a tourniquet can effectively control exsanguination from an extremity. Deeper wounds in noncompressible areas such as the anatomic junctions of the neck, upper chest, and groins may benefit from packing to exert intrinsic compression.

When internal bleeding is suspected as the cause of hemorrhagic shock, operative management is typically required. The initial evaluation and diagnostic workup will guide which body cavity is of focus. Anterolateral thoracotomy can provide broad exposure to identify and control bleeding in the chest. Midline laparotomy provides rapid entrance and exposure to the abdominal cavity. When hemorrhage is from the pelvis, a lower midline incision can facilitate entrance to the preperitoneal space, which can be packed as a temporizing measure.

OBSTETRIC HEMORRHAGE

Epidemiology

Obstetric hemorrhage is the leading direct cause of maternal death worldwide, and postpartum hemorrhage accounts for approximately 25% of all cases.[29–31] In 2017, approximately 295,0000 women died from preventable causes related to pregnancy and childbirth. Maternal mortality is defined as the death of a woman during pregnancy and within 42 days following termination of pregnancy regardless of the cause, duration, or site of the pregnancy.[32]

The main categories of obstetric hemorrhage include vaginal bleeding in early pregnancy (less than 20 weeks); antepartum hemorrhage (AH) or vaginal bleeding after 20 weeks; and postpartum hemorrhage (PPH), massive blood loss after delivery, defined as greater than 1000 mL or bleeding associated with signs/symptoms of hypovolemia within 24 hours of birthing regardless of delivery route.[33] **Table 3** presents the main causes and incidence of obstetric hemorrhage.

In the United States, 11.4% of all pregnancy-related mortality was due to obstetric hemorrhage,[34] but 94% of all maternal deaths occur in LMICs.[35] And among all maternal deaths related to obstetric hemorrhage, PPH is responsible for more than three-fourths of them and, with an increasing global incidence of 3% to 10% of all deliveries, was one of the top 5 causes of maternal mortality in both LMICs and HICs.[29] The risk of death from PPH is much higher in LMICs, although, for a multitude of reasons, some of which relate to blood transfusion availability as well as health

Table 3
Classification of obstetric hemorrhage by incidence rates and specific cause

Classification of Obstetric Blood Loss	Incidence of Bleeding	Specific Cause of Hemorrhage
Vaginal bleeding in early pregnancy	20%–40% of all pregnancies[42,87]	Ectopic pregnancy Abnormal implantation: cesarean scar/cervical pregnancy Miscarriage Unsafe abortion Cervical/vaginal/uterine pathology Molar pregnancy/choriocarcinoma
Antepartum hemorrhage	2%–6% of all pregnancies[37–39]	Placenta previa Placental abruption Placenta accreta spectrum Uterine rupture Vasa previa Amniotic fluid embolism
Postpartum hemorrhage	5%–18% of all pregnancies[88–90]	Uterine atony Retained placenta Cervical/vaginal lacerations Coagulopathy/disseminated intravascular coagulopathy Uterine inversion

infrastructure and workforce.[30] Mortality has been noted to be 2- to 3-fold higher in northern Africa, for example, compared with the 16.3% in HICs.[29] Further, mortality is likely inadequate to measure the true impact—17.6% of postpartum hemorrhage episodes result in severe maternal outcomes as measured by death or a "near miss" of resultant organ-system dysfunction.[36]

Initial Evaluation

For AH in early pregnancy, the history and extent of bleeding should be determined. A detailed history will solicit symptoms that indicate significant blood loss, including passage of blood clots or blood soaking through their clothes, lightheadedness, significant cramping, and passing of tissue. A physical examination should include an examination of any tissue and abdominal and pelvic examination. Uterine size (an estimate of gestational age) and the presence of midline or lateralized tenderness should be determined. A speculum examination should determine the amount of bleeding; the appearance of the cervix; presence of cervical dilation; or any signs of laceration/injury, masses, or infection. Laboratory studies should include a complete blood count, a qualitative or preferably quantitative human chorionic gonadotropin level, and blood grouping. A transvaginal and transabdominal ultrasound should assess the uterus, adnexa, the presence of masses, fetus and fetal heart rate, and free fluid. For second and third trimesters AH, evaluation consists of assessing the extent of bleeding, presence of pain, hemodynamic stability, assessment of fetal viability, and well-being (fetal nonstress test, ultrasound, biophysical profile). An abdominal examination should assess for uterine size and tenderness. A speculum examination should assess the cervical os for the presence of amniotic fluid, bleeding, or fetal membranes/parts/placental tissue. Ultrasound should confirm the location of the placenta, amniotic fluid, fetal gestational age, and estimated fetal weight.[37–39]

In PPH, all blood loss should be quantified. The patient should be monitored for hemodynamic stability and oxygenation. On examination, look for significant vaginal or cervical lacerations, even in patients who underwent cesarean delivery, as cervical dilation and descent can cause lacerations. Repeat examination even if performed at birth time. Assess the uterus for tone, retained placenta, abnormal placentation (placenta accreta spectrum), and uterine inversion. If the patient presents with anal pain out of proportion, a rectal examination should be performed to look for vaginal hematoma. A FAST examination can be performed to evaluate the abdomen, and uterine tone should also be assessed during this examination.[33,40]

Delayed response to change in vitals after delivery is a common factor of preventable maternal death.[41] Assume progressively increasing heart rate and decreasing blood pressure are due to blood loss/hypovolemia until these causes are positively excluded. Some patients may only present mild signs of shock such as mild tachycardia and mild hypotension. If the patient is potentially unstable, moving them to an operating room is the safest option in case further action is needed. Deterioration of maternal vital signs out of proportion to vaginal bleeding suggests intraperitoneal or retroperitoneal bleeding (eg, ruptured uterus, hepatic rupture due to preeclampsia, expanding vaginal hematoma).

Diagnosis

Vaginal bleeding in early pregnancy could represent a threatened abortion, incomplete abortion, or complete abortion. All patients with early pregnancy bleeding and pain should be assumed to have an ectopic pregnancy until proved otherwise. A pregnancy should be seen within the uterus by transvaginal ultrasound once the human chorionic gonadotropin (HCG) level is greater than 2000 to 3500 IU. A decreasing beta-HCG is consistent with failed pregnancy.[42–44]

For second and third trimester bleeding, patients should be assessed for placental location and placental abruption. Placenta previa generally is painless, and a placental abruption typically presents with vaginal bleeding, uterine tenderness, and uterine contractions with or without abnormalities on fetal heart rate. Ultrasound has low sensitivity for placental separation. Ultrasound evaluation of uterine rupture would show free fluid in the abdomen with possible extravasation of the fetus. Management depends on gestational age, cause and severity of bleeding, and maternal and fetal status.[45,46]

In PPH, timelines in its recognition, determination of cause, and initiating treatment are critical. Although challenging in the obstetric setting, careful quantification of blood loss is recommended.[47] In most cases, a vaginal and bimanual examination can determine the cause of postpartum hemorrhage. Patients should be assessed for coagulopathy with thromboelastography when available or use a simple red top tube to assess for clotting ability. FAST can be used to assess shock signs with no vaginal bleeding associated. However, because sensitivity is low, a negative result should not rule out internal bleeding.[48,49]

Management

Ruling out life-threatening vaginal bleeding is the first step in working up first-trimester acute hemorrhage. Miscarriages can be managed expectantly, medically, or surgically with manual vacuum aspiration or suction dilation and curettage.[50] Surgical evacuation is indicated in patients who are actively bleeding and unstable. A ruptured ectopic pregnancy with evidence of intraabdominal bleeding mandates surgical management and gynecologic consultation when available. Laparoscopy or laparotomy must not be delayed in unstable patients with suspected ectopic pregnancy. In all cases of

hemorrhage, management involves supportive care with intravenous fluids, checking blood levels, and transfusing as indicated.[42–44]

For second and third trimester bleeding, rapid obstetric consultation should be obtained in case cesarean delivery is needed. In hemodynamically unstable patients and in patients with cardiac arrest displacing the uterus to the patient's left side significantly improves cardiac output. Substantial changes in vital signs may not occur until more than 20% of total blood volume has been lost due to the hypervolemia and normal physiology of pregnancy. Fetal heart rate monitoring, when appropriate based on viability (>20 weeks gestation), is essential for determining the condition of the fetus. RhD-negative women with abdominal or pelvic trauma or with vaginal bleeding should receive anti-D immune globulin, per standard protocols.

Treatment goals for PPH are to restore circulatory volume, maintain tissue oxygenation, reverse or prevent coagulopathy, and eliminate the obstetric cause. Uterine atony is the most common cause of PPH. In this case the patient should have her bladder emptied and fundal and bimanual uterine massage should be attempted (misoprostol, oxytocin/carbetocin, methergine, hemabate, tranexamic acid). If the atony is persistent, uterine tamponade methods should be attempted such as an intrauterine balloon (condom balloon or Bakri), gauze packing, or suction compression (Jada). Some patients may require an operation where uterine-sparing surgery can be attempted with ligation of the hypogastric, the B-Lynch suture, O'Leary suture, or placement of a uterine artery embolization by interventional radiology. Ultimately, a peripartum hysterectomy may be necessary to control blood loss.[33,51–53]

Retained products of conception are more common after a vaginal birth but can happen after any delivery. If the first 2 fail, the procedure is performed manually, with forceps, curettage, or a suction catheter. An unstable patient should be examined for uterine rupture, a rare complication that can happen even with vaginal births when there is instrumental delivery or induced labor. Persistent pain and vaginal bleeding after drugs should serve as an alert for this complication, and the management is usually hysterectomy. Blood might accumulate in the retroperitoneum or inside the uterine cavity and not be seen after the wound is closed. If the patient presents with laceration, a repair should be made.[51] A uterine inversion should be identified before placental separation and manually replaced. In rare cases muscle relaxing agents or surgical intervention is necessary.[54]

Blood loss should always be measured. It can be done by weighing pads soaked with blood subtracting the weight of a dry pad.[50] In case of blood loss exceeding 1.5 L, the physician should ask for complete blood count, type and crossmatch, coagulation studies, thromboelastographic examinations, and proceed with blood transfusion. Consider autologous transfusion early, either in vaginal or cesarean delivery. Blood can be collected after delivery of the placenta, and an effort should be made to avoid contamination with fecal material or amniotic fluid.[55] For PPH, an aggressive transfusion approach can be used, and there is no current specific guideline. An approach used by the Stanford University Medical Center is the use of an initial package consisting of 6 units RBCs, 4 units fresh frozen plasma, and 1 apheresis platelet unit and a hemoglobin target of greater than 7 g/dL.[56]

In general, management of all of these conditions is the same across low and high-resource settings. Challenges within low-resource settings include delays in access to care, with patients presenting in late stages of hemorrhagic shock.[57] There are often challenges in access to medications, anesthetists, specialist health care providers such as obstetricians and gynecologists, blood for transfusion, and diagnostic tests including blood work and imaging.[58,59] Important adaptations in a low-resource setting might include transferring to higher level of care, use of ketamine for

anesthesia, reliance on affordable temperature stable medications such as misoprostol and tranexamic acid, task shifting to allow nurses and mid-levels perform manual vacuum aspiration, uterine tamponade with a condom balloon, and autologous blood transfusions using devices such as the hemafuse.[60–62]

UPPER GASTROINTESTINAL BLEEDING

Epidemiology

Upper gastrointestinal bleeding (UGIB) is a common source of hemorrhage that occurs in the proximal gastrointestinal tract. Hospitalization rates for UGIB are 6 times higher than lower GI bleeding and result in substantial morbidity, mortality, and medical expense.[63–65] The mortality varies from 5% in the United States to 30% in Sub-Saharan Africa,[66] with the higher rates attributed to delay in diagnosis, treatment, and inadequate infrastructure, including access to blood.[67]

Multiple conditions can lead to a UGIB, and these vary in prevalence across the world. For example, the 2 major causes of severe bleeding from UGIB are peptic ulcer disease and esophagogastric varices. Peptic ulcers are typically the most common cause of hemorrhage in the upper GI tract, and gastric ulcers are the most common. The proportion of UGIB due to peptic ulcers ranges as high as 30% to 65% in some studies from Egypt, Brazil, and India. Varices occur due to portal hypertension, which is another major cause of UGIB. In many African studies, esophageal varices were found to be the main cause of UGIB.[67,68] Some of these variations may be related to the prevalence of infections such as hepatitis B, hepatitis C, and schistosomiasis that are endemic in many parts of the world, particularly LMICs, and can result in cirrhosis.[67] Most patients with cirrhosis develop varices, with an annual hemorrhage rate of 5% to 15%[69] and a mortality rate around 20% with active bleeding.[67,69] **Table 4** outlines common causes of UGIB and prevalence from studies across the world.

Initial Evaluation

Most commonly, patients with UGIB present with hematemesis, which is vomiting of blood and/or melena, which are black, tarry stools, the result of blood that has traveled through the GI tract. It is worth noting that part of the patients might present with hematochezia, or bloody bowel movements, even though this sign is more common in LGIB. Patients with variceal cause usually present more to care with active bleeding compared with nonvariceal causes, such as ulcerations and erosive lesions.[70]

The goal of the initial evaluation is to assess the severity of the bleed, identify potential sources of the bleed, and determine other conditions present that may affect management. Rectal examination can help assess stool color (melena vs hematochezia vs brown). A nasogastric tube may provide evidence of upper GI bleeding when the presenting sign is melena or hematochezia. History is a key component—up to 60% of patients with a history of a previous UGIB are bleeding from the same lesion.[71]

Diagnosis

Endoscopy is often diagnostic and therapeutic. Although endoscopy should be performed as soon as possible, preferably within 24 hours of UGIB, its performance at any point can decrease patient mortality.[67] Nonetheless, there is scant availability of endoscopy in many of the world's rural settings.[72] As such, many GI bleeds remain unexplained after clinical and/or endoscopic evaluation (where available) and are often called "undetermined" or "obscure GI bleeding." Advances in diagnostic imaging have steadily decreased the prevalence of obscure GI bleeding but most settings across

the world lack access to these diagnostics.[73,74] A CT angiogram has high sensitivity and specificity for bleed location and can further guide therapeutic options when available.

Management

As in all cases of hemorrhagic shock, the key management principles are to stop the bleeding and replace lost blood volume. In the process of doing this, special attention should be given to airway status, monitoring of vital signs and cardiac rhythm, urine output, and nasogastric output. All patients with suspected or known severe bleeding should be started on high-dose proton pump inhibitors.[75] For patients with known or suspected esophagogastric variceal bleeding, the goal of therapy is to control acute hemorrhage and to prevent its recurrence.[76] These patients should receive somatostatin or analogues such as octreotide to decrease portal pressure and prophylactic antibiotics covering gram negatives.[69]

Judicious blood transfusion is important with a hemoglobin target of 7 to 9 g/d. A transfusion target of 9 to 11 g/dL in patients with cirrhosis is associated with increased mortality, possibly due to an increased hepatic venous pressure gradient, which can lead to increased variceal bleeding.[77]

Stopping the bleeding requires first making a diagnosis and localizing the bleed. Gastroenterologists and interventional radiologists, where available, play a critical role, as therapies are more directed and less morbid than surgical exploration. Emergency surgery for UGIB may be indicated in low-resource settings when there is limited capacity for nonsurgical treatment.[72] Endoscopy offers many advantages including diagnosis and therapy with thermal coagulation, hemostatic clips, and injection therapy.[75] For variceal hemorrhage, esophageal balloon tamponade can be used as a temporizing measure before definitive therapy.[69] Esophageal banding and scleral therapy are the first line of treatment.[67,78] Although transjugular intrahepatic portosystemic shunting (TIPS) is often the fallback for severe variceal bleeding, its availability across the world is limited. Surgical shunts, although effective at stopping bleeding, have high mortality rates and have largely been supplanted by TIPS, where available.

Table 4
Most common causes of upper gastrointestinal bleeding worldwide

Most Common Causes	Prevalence (%)
Gastric and/or duodenal ulcers	6–65
Esophagogastric varices	12.8–56.3
Severe or erosive gastritis/duodenitis	2.5–12.9
Severe or erosive esophagitis	0.3–14.7
Mass lesions	1.7–8
Angiodysplasia	0.5–4.7
Mallory-Weiss syndrome	1–5
Unknown source	1–38

Unknown source is * defined by normal findings at the time of endoscopy after episode of bleeding and unknown causes for active bleeding.
Data from Refs.[67,68,70,74,91–93]

GLOBAL BLOOD SUPPLY

Approximately 3% of severely injured trauma patients will need a massive blood transfusion, and up to 16.5% of patients with postpartum hemorrhage will require a high-volume transfusion and surgical intervention.[79] Although patients in hemorrhagic shock urgently need blood for transfusion, there is a shortfall that makes transfusion scarce or impossible in much of the world. In fact, there is a 114 million unit shortage of blood worldwide annually, and most of the deficit is located in Sub-Saharan Africa, South Asia, and Oceania.[80] With scarcity, blood typically goes to treating more chronic conditions, including oncologic needs and pediatric anemias; lesser amounts are available for emergency obstetric hemorrhage and trauma patients.[81]

The reasons for scarcity are multifactorial. A consistent supply of blood requires complex logistics spanning a continuum from community engagement and donor recruitment to blood collection, blood testing, blood processing, administration, and hemovigilance. With underfunded health systems comes underfunded blood systems and significant challenges with maintenance of each part of this continuum.[82] Further, some challenges specific to low-resource environments would present barriers even with the best resources—high levels of malnutrition drive high levels of chronic anemia, and endemic levels of hepatitis B, C, and human immunodeficiency virus render a significant portion of the population unsuitable for blood donation.

A significant portion of the blood supply in Sub-Saharan Africa and South Asia remains with whole blood as the primary product for transfusion; this presents logistical challenges in cases of providing appropriate resuscitation, as the provision of a 1:1:1 ratio of packed red blood cells to plasma to platelet transfusion requires an organized, well-functioning blood bank with adequate stores of each component and the workforce to thaw, prepare, and deliver adequate quantities of each component for transfusion, on-demand.[17]

Although further investment in health and blood systems is urgently necessary—allowing for optimizations along the entire continuum of transfusion—policy-level changes may also be required that decentralize blood systems and allow for greater stewardship at the community level. Attention must be paid to "disruptive" solutions that can provide more immediate relief in cases of extreme scarcity. Promising strategies include the concept of community walking blood banks, where blood is collected on-demand, tested with rapid diagnostic testing kits, and transfused to those in need; this would be a civilian adaptation of an innovation refined over the past 2 decades by American and Scandinavian militaries.[15,83] Drone-based blood delivery, where blood collection centers are paired with unmanned aerial vehicles for delivery to distant hospitals without blood stores are another recent strategy showing promise in low-resource, blood-deficient areas.[84] Finally, intraoperative autotransfusion—where a patient's blood is collected, filtered, and transfused back to the same patient—is not a new concept in the high-income or low-income setting but is now receiving renewed attention from the low-cost innovation sector.[85] The Hemafuse device by Sisu Global Health is a system designed for the low-resource environment and has shown promise in treating obstetric hemorrhage from ectopic pregnancy and splenic rupture.[86]

SUMMARY

Critical care has and continues to play a key role in the immediate identification of both insidious and overt blood loss, most commonly in the settings of trauma, obstetric hemorrhage, and upper gastrointestinal bleeding. The burden and epidemiology of hemorrhage vary by context, and management depends on the availability of blood

products, trained personnel, and the broader health care infrastructure. Hemorrhage remains the cause of almost half of the deaths by trauma, and there is a massive shortage of blood products in many parts of the world, especially in lower-income countries. It is imperative that action is taken soon to decrease the burden of bleeding worldwide and that new alternatives for blood transfusion become readily available to the centers in need.

CLINICS CARE POINTS

- The signs and symptoms of hemorrhagic shock are often subtle, and early diagnosis is critical to prevent the rapid consequences of unrecognized or unchecked bleeding.
- In the setting of trauma, in addition to the key management principles of stopping the bleeding and replacing lost blood volume, identifying hemodynamically significant internal bleeding in all potential spaces will be crucial to guiding further management.
- Postpartum hemorrhage is the leading cause of maternal death worldwide, and its treatment should aim to restore circulatory volume, maintain tissue oxygenation, reverse or prevent coagulopathy, and eliminate the cause of obstetric bleeding.
- Although endoscopy within 24 hours is the standard of care for diagnosis and treatment of upper gastrointestinal bleeding, where endoscopy is not readily available, stratified treatment algorithms established by local governing bodies will guide management to reduce mortality.
- Blood scarcity influences blood administration variably depending on context, but can lead to a redirection of limited available blood products to patients with less urgent conditions, resulting in a large unmet need for blood products for patients experiencing traumatic or obstetric hemorrhage.

DISCLOSURE

The authors have nothing to disclose.

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