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ATS Core Curriculum 2020

Adult Critical Care Medicine

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ABSTRACT

The American Thoracic Society Core Curriculum updates clinicians annually in adult and pediatric pulmonary disease, medical critical care, and sleep medicine, in a 3- to 4-year recurring cycle of topics. These topics will be presented at the 2020 International Conference. Below is the adult critical care medicine core including complications of chemotherapy, acute-on-chronic liver failure, alcohol withdrawal syndrome, mechanical circulatory support, direct oral anticoagulants, upper gastrointestinal hemorrhage, and vasopressor selection.

Keywords:
core curriculum; critical care medicine; clinical review

KEY POINTS

- All classes of conventional chemotherapy and immunotherapy agents can be associated with life-threatening side effects, including pulmonary toxicity, neurotoxicity, and cardiotoxicity. The intensive care unit physician must be prepared to recognize and manage these toxicities in close collaboration with the treating oncologist.
- Prompt recognition and multidisciplinary management of acute-on-chronic liver failure and its triggering event(s) are crucial in preventing high short-term mortality and multiple organ failure.
- A severe alcohol withdrawal syndrome, like many critical illnesses, is best managed through early identification and prevention. Once manifest, first-line therapy for severe withdrawal remains benzodiazepines with varying degrees of evidence supporting phenobarbital, dexmedetomidine, and propofol as adjuncts.
- There are many mechanical circulatory support devices available that differ by ventricle supported, blood flow capability, and ability to incorporate an oxygenator for respiratory support.

- In cases of life-threatening bleeding, direct oral anticoagulants should be discontinued and reversal of the anticoagulated state should be pursued; this may range from dialysis to administration of clotting factor products to agent-specific reversal drugs, where available.
- Successful management of upper gastrointestinal hemorrhage requires an interdisciplinary approach of hemodynamic stabilization, medical management, endoscopic intervention, and, in refractory cases, vascular procedures.
- Vasopressors are indicated when blood pressure and tissue perfusion remain insufficient following intravascular volume resuscitation; options include catecholamines, vasopressin, and angiotensin II.

The American Thoracic Society (ATS) Core Curriculum updates clinicians annually in adult and pediatric pulmonary disease, critical care, and sleep medicine, in a 3- or 4-year recurring cycle of topics. The 2020 course was intended for presentation in May during the annual International Conference. Because of the coronavirus disease (COVID-19) pandemic, the annual conference was canceled, and the talks are available as part of the ATS 2020 Virtual Meeting. The following is a concise review of the critical care topics covered in the 2020 ATS Core Curriculum.

COMPLICATIONS OF CHEMOTHERAPY

Mary Elizabeth Card and R. Scott Stephens

The mainstays of cancer treatment are conventional chemotherapy and, increasingly, immunotherapy and immune effector cell therapy. These therapies are associated with life-threatening side effects, such as pulmonary toxicity, neurotoxicity, and cardiotoxicity (Figure 1).

GENERALIZED TOXICITY

Several chemotherapy agents can induce toxicity immediately after administration.
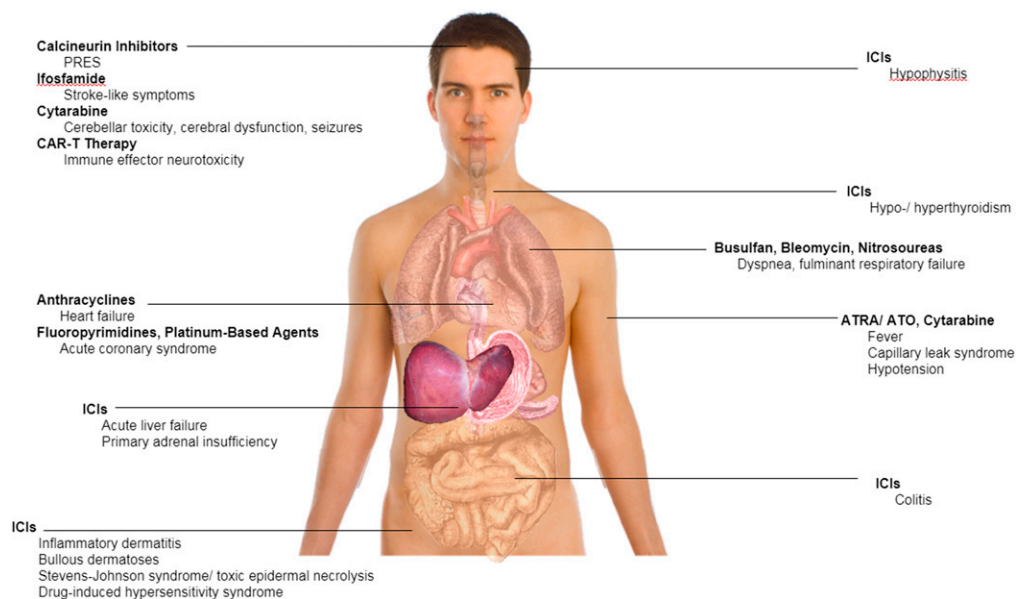

Figure 1. Complications of chemotherapy. ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CAR-T = chimeric antigen receptor T cell; ICIs = immune checkpoint inhibitors; PRES = posterior reversible leukoencephalopathy syndrome.

Patients with acute promyelocytic leukemia treated with all-trans retinoic acid (ATRA) and arsenic trioxide can rapidly develop ATRA syndrome, a severe inflammatory response caused by rapid differentiation of myeloid cells. Presentation includes fever and capillary leak syndrome resulting in hypotension and pulmonary edema. Treatment requires rapid initiation of high-dose steroids (1, 2). In general, ATRA/arsenic trioxide should be continued. ATRA syndrome is difficult to distinguish from septic shock; empiric antibiotics should be administered. Cytarabine syndrome, seen with cytarabine-containing induction regimens for acute myeloid leukemia, can also present with capillary leak and hypotension. Treatment includes steroids and supportive care.

PULMONARY TOXICITY

Adverse events range from subacute shortness of breath to fulminant respiratory failure (1). Some agents, such as bleomycin and busulfan, are associated with predictable, dose-dependent toxicities, but many agents cause idiosyncratic effects. Diagnosis depends on presentation, chest imaging, and exclusion of alternative diagnoses. The offending agent should be discontinued, and steroids should be administered, although efficacy is limited. Steroid dose and duration are not well established; a generally accepted regimen is 0.5–1 mg/kg/d of prednisone (or equivalent) for 8–12 weeks (1).

NEUROTOXICITY

Life-threatening neurotoxicity includes posterior reversible leukoencephalopathy syndrome, seizures, cytarabine neurotoxicity, and encephalopathy (3, 4). Calcineurin inhibitors (e.g., tacrolimus, cyclosporine) are common precipitators of posterior reversible leukoencephalopathy syndrome (5), which presents with encephalopathy, seizures,

hypertension, and magnetic resonance imaging abnormalities. The triggering agent should be discontinued and blood pressure controlled. High-dose busulfan, used in the conditioning regimen for hematopoietic stem cell transplant, causes seizures in up to 10% of patients. Ifosfamide can cause a stroke-like presentation with seizures, confusion, cerebellar dysfunction, and focal motor-sensory deficits, typically reversible with methylene blue. Cytarabine can also cause acute cerebellar toxicity, cerebral dysfunction, and seizures.

CARDIOTOXICITY

Cardiac toxicity, including acute coronary syndrome (ACS) and dilated cardiomyopathy leading to cardiogenic shock, is a leading cause of long-term morbidity and mortality in patients with cancer (6). ACS may be the result of chemotherapy-induced stress in the setting of preextant risk factors, but some chemotherapeutic agents, most notably fluoropyrimidines and platinum-based agents, have been reported to trigger ACS. (6) Treatment of ACS is complicated by the prevalence of coagulopathies and thrombocytopenia in this population. Anthracyclines (e.g., doxorubicin) are known to cause heart failure, which should be treated according to typical standards of care (6).

IMMUNOTHERAPY COMPLICATIONS

Immune checkpoint inhibitors (ICIs) are used to treat an increasing number of malignancies. ICIs can affect any organ system, with the most common immune-related adverse events (irAEs) being cutaneous, gastrointestinal, hepatic, endocrine, and pulmonary toxicities. Toxicities are graded on a scale of 1–4; grades 3–4 indicate severe or life-threatening reactions.

Grade 3 or 4 cutaneous toxicities have an incidence of 1–3% and

include inflammatory dermatitis, bullous dermatoses, Stevens-Johnson syndrome/toxic epidermal necrolysis, and drug-induced hypersensitivity syndrome. High-grade gastrointestinal toxicity affects about 15% of patients, presents 5–10 weeks after ICI initiation, and includes severe colitis and acute liver failure. Endocrine toxicities include primary hypo-/hyperthyroidism, primary adrenal insufficiency, and hypophysitis. Severe pneumonitis is reported to occur in approximately 2% of patients treated with ICIs, although the true incidence may be higher. Patients typically present 2–24 months after ICI initiation with dyspnea, cough, fever, and chest pain and can develop fulminant respiratory failure. Chest computed tomography findings typically demonstrate ground-glass opacities.

Regardless of organ system involved, the diagnosis of irAEs remains one of exclusion. Initial treatment for grade 3 and 4 toxicities should include at least temporary cessation of immunotherapy and 1–2 mg/kg/d intravenous methylprednisolone, tapering over at least 4 weeks or based on symptom resolution. In steroid-refractory cases, other immunosuppressive agents (such as intravenous immunoglobulin, cyclophosphamide, mycophenolate mofetil, or infliximab) can be considered. For grade 4 irAEs, ICI treatment should be permanently discontinued. For grade 3 or less, the risks versus benefits of resuming ICIs must be weighed in consultation with an oncologist (7).

Chimeric antigen receptor T-cell therapy is yet another novel anticancer therapy. Common toxicities include cytokine release syndrome and immune effector neurotoxicity. Treatment for cytokine release syndrome consists of supportive care, with anti–interleukin 6 agents (e.g., tocilizumab, an anti–interleukin 6 monoclonal antibody) and steroids reserved for severe cases. In contrast, tocilizumab is ineffective in neurotoxicity, and steroids are the mainstay of therapy (8).

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ACUTE–ON–CHRONIC LIVER FAILURE

Amjad Kanj and Alice Gallo de Moraes

Acute-on-chronic liver failure (ACLF) refers to profound hepatic decompensation and organ failure in patients with preexisting liver disease. It is associated with high short-term mortality and requires prompt recognition and aggressive management (1). ACLF is often triggered by sepsis, gastrointestinal bleeding, or drugs/toxins. Severity largely depends on the host's immune dysfunction and inflammatory response to the inciting event (2), which often cannot be identified (1). The management of ACLF is summarized in Table 1.

SEPSIS AND ACLF

Sepsis is a common trigger for ACLF. When suspected, an infectious workup including evaluation for spontaneous bacterial peritonitis must be performed (2). Antibiotics should be started immediately and tailored according to culture results and local resistance patterns. Empiric antifungal therapy should be considered in patients without clinical improvement after 48–72-hours of broad-spectrum antibiotics (2). Balanced crystalloids, such as lactated Ringer's, are recommended for initial fluid resuscitation (3). Albumin is recommended in patients with spontaneous bacterial peritonitis and after large-volume paracentesis (4). Norepinephrine (NE) remains the preferred vasoactive drug and should be titrated for a mean arterial pressure of 60–65 mm Hg (2, 4).

ORGAN FAILURE IN ACLF

Extrahepatic organ failure is a hallmark of ACLF. The definitions of ACLF and organ failure vary among international societies, but the proposed management is similar (4, 5).

Renal Failure

Renal failure (RF) is the most frequent organ dysfunction in ACLF. Serum creatinine and, to a lesser extent, cystatin C overestimate renal function in ACLF. Urine output remains an early sensitive marker for RF. Management of RF depends on the etiology. In type 1 hepatorenal syndrome, vasoconstrictors and 25% albumin should be used. NE is the vasoconstrictor of choice when terlipressin is not available. Alternatively, the combination of octreotide, midodrine, and albumin may be used but should be switched to terlipressin or NE if kidney function fails to improve within 3 days. In patients with refractory volume overload and electrolyte imbalances, renal replacement therapy can be initiated until prognosis is determined (4).

Hepatic Encephalopathy

Hepatic encephalopathy is graded using the West Haven criteria; patients with grade 1 encephalopathy exhibit mild symptoms,

Table 1. Management of ACLF, its triggers, and associated organ failure

ACLF	Management
Triggers	
Sepsis	Sources: consider blood, urine, lung, ascitic fluid, and pleural fluid
	Fluids: 30 ml/kg LR or PlasmaLyte
	Antibiotics: empiric broad-spectrum + antifungals if no improvement
	Vasopressors: norepinephrine ± vasopressin and hydrocortisone
Gastrointestinal bleed	Blood products, antibiotic prophylaxis, octreotide, definitive therapy
Toxins (e.g., alcohol)	Abstinence ± steroids
Organ failure	
Renal failure	Suspected type 1 HRS: Albumin + terlipressin (not available in the United States) or NE, OR albumin + midodrine + octreotide
	RRT in nonresponders who are potential liver/kidney transplant candidates
	Nephrology consultation
Hepatic encephalopathy	Lactulose ± rifaximin
	Intubation if GCS <8
	Aspiration precautions
Coagulopathy	Target Hb >7 mg/dl
	Target platelets >50 × 10^9/L if bleeding or before minimally invasive procedures
	Target fibrinogen >1.5 g/L if bleeding or before surgery
Other	
Consultations	Hepatology consultation
	Palliative care consultation
	Early referral to a liver transplant center

Definition of abbreviations: ACLF = acute-on-chronic liver failure; GCS = Glasgow Coma Scale; Hb = hemoglobin; HRS = hepatorenal syndrome; LR = lactated Ringer's; NE = norepinephrine; RRT = renal replacement therapy.

whereas those with grade 4 are comatose (3). Lactulose should be initiated and titrated to 2–3 bowel movements per day. Head imaging and electroencephalography should be considered to exclude structural abnormalities and seizures when encephalopathy is severe or when there is lack of response to treatment (4). Aspiration precautions are important in those at high risk. Endotracheal intubation is recommended for Glasgow Coma Scale <8, and short-acting, nonbenzodiazepine medications are preferred for sedation (4).

Coagulation Dysfunction

The impact of liver disease on coagulation is variable, and partial thromboplastin time (PTT), international normalized ratio (INR), fibrinogen level, and bleeding time

do not accurately reflect the risk of bleeding. Venous thromboembolism prophylaxis should be considered in the absence of active bleeding. There is no role for prophylactic transfusion of blood products in patients with abnormal coagulation parameters who are not actively bleeding (5). Transfusion targets are listed in Table 1. Unlike disseminated intravascular coagulation, coagulopathy of liver failure presents with normal or elevated factor VIII level with no schistocytes on peripheral smear. Viscoelastic testing can assess coagulopathy, but its role outside liver transplantation and surgery remains controversial (5).

PROGNOSIS OF ACLF

The 28-day mortality from ACLF approaches 80% among patients with ≥3 organ failures, and early referral to a transplant center is recommended. Validated scores, such as the CLIF-C (Chronic Liver Failure Consortium) ACLF, help define futility of intensive care support (6). A palliative care approach should be considered in patients with ACLF who continue to deteriorate despite 3–7 days of intensive care support and for whom organ transplant is not an option (6).

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MANAGEMENT OF ALCOHOL WITHDRAWAL SYNDROME

Dylan Lovin and Matthew J. Leveno

Alcohol use disorder (AUD) affects 20–42% of hospitalized patients. Most hospitalized patients with AUD will not develop symptoms of withdrawal sufficient to warrant medications, but 5–10% of those that do will require critical care (1, 2). The four most common presentations of alcohol withdrawal are discussed below.
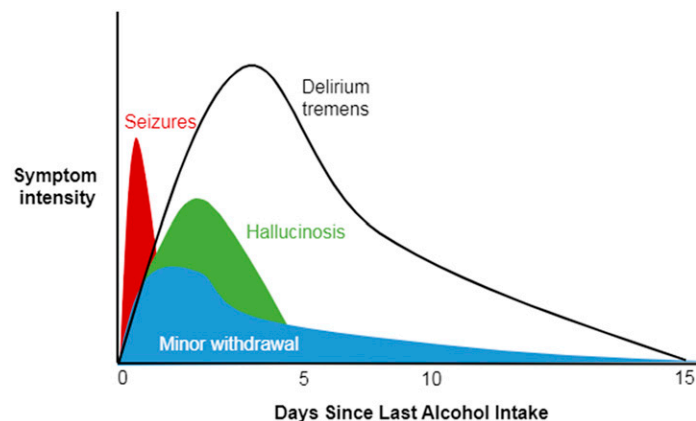
Figure 2. Onset of alcohol withdrawal syndromes relative to last alcohol intake.

UNCOMPLICATED ALCOHOL WITHDRAWAL

Uncomplicated alcohol withdrawal, also called simple or minor withdrawal, typically occurs within 6–24 hours of last alcohol intake (Figure 2). It is characterized by agitation, insomnia, headache, tremor, nausea/vomiting, and autonomic hyperactivity. Importantly, patients with uncomplicated withdrawal have a preserved mental status. Symptom-triggered benzodiazepine (BZD) administration using a validated withdrawal assessment tool is the treatment of choice (3). Patients with uncomplicated withdrawal who are treated with BZDs are far less likely to develop delirium tremens (4).

ALCOHOL HALLUCINOSIS

Alcohol hallucinosis is characterized by visual, auditory, or tactile hallucinations that develop 12–24 hours after last alcohol intake (Figure 2). Patients have an awareness of their hallucinations, and their orientation and vital signs are generally normal.

ALCOHOL WITHDRAWAL SEIZURES

Alcohol withdrawal seizures occur in a minority of patients experiencing withdrawal and may be the first manifestation of withdrawal. They typically occur within 6–48 hours following last alcohol intake (Figure 2). Although alcohol withdrawal is a common cause of a new-onset seizure, the diagnosis of an alcohol-related seizure is one of exclusion (5). Alcohol withdrawal seizures are most often tonic-clonic and occur in self-limited clusters of 1–3 seizures. Focal seizures and status epilepticus are atypical. BZDs are first-line therapy. A single dose of lorazepam is often sufficient to prevent additional seizures (6). However, patients remain at risk for other withdrawal symptoms, and 30% will develop delirium tremens if untreated.

DELIRIUM TREMENS

Delirium tremens represents the most severe form of alcohol withdrawal. The signs and symptoms of delirium tremens include severe delirium, autonomic hyperactivity, and hallucinations. BZDs remain first-line therapy. Although there is no clear first choice of BZD, drugs with a rapid onset of action and a favorable pharmacokinetic profile for the individual patient are preferred. For patients that fail to respond adequately to BZDs, common adjuncts include propofol, dexmedetomidine, and phenobarbital (7). In the

nonintubated patient, dexmedetomidine and phenobarbital are useful agents. With more than 100 years of clinical experience, low cost, and multiple favorable studies, phenobarbital appears to be the adjunct of choice (8).

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MECHANICAL CIRCULATORY SUPPORT

Valerie E. M. Griffeth and Bishoy Zakhary

CARDIOGENIC SHOCK

Cardiogenic shock (CS) is defined as a reduced cardiac index (typically <1.8 L/min · m²) with end-organ hypoperfusion and adequate filling pressures. Outcomes are poor, with in-hospital mortality greater than 50% (1). Although inotropic infusions are often first-line therapy, failure to reverse the shock state necessitates mechanical circulatory support (MCS). Early identification of patients with severe or persistent shock may facilitate early initiation of MCS and improve outcomes.

MECHANICAL CIRCULATORY SUPPORT DEVICES

The goals of MCS are to supplement native cardiac function and restore end-organ perfusion, decompress the failing ventricle, and increase coronary artery perfusion. Although devices differ in mechanism of action, the majority reduce ventricular preload and afterload while increasing perfusion to the systemic circulation. For patients with reversible or treatable etiologies of CS, this support can facilitate definitive treatment, such as coronary intervention in ischemic disease or ablation therapy in refractory arrhythmia.

Multiple devices are available to support the acutely failing heart. For patients with isolated left ventricular failure, options include the intraaortic balloon pump

Table 2. Comparison of commonly used mechanical circulatory support devices

	Ventricle Supported	Circuit Configuration	CO (L/min)	Effect on				Accommodates Oxygenator
				RV Preload	RV Afterload	LV Preload	LV Afterload	
IABP	LV	LV → Ao	0.5–1.0	—	—	—	↓	No
Impella	LV	LV → Ao	Up to 5.0	—	—	↓	—	No
Impella RP	RV	RV → PA	Up to 4.0	↓	—	↑	—	No
TandemHeart	LV	LA → Ao	Up to 4.0	—	—	↓	↑	Yes
Tandem protek duo	RV	RA → PA	Up to 4.0	↓	↑	↑	—	Yes
Centrimag	RV —	RA → PA	>5.0	↓	↑	—	—	Yes
	— LV	LA → Ao		—	—	↓	↑	
VA ECMO	RV & LV	RA → Ao	>5.0	↓	—	↑	↑	Required

Definition of abbreviations: Ao = aorta; CO = cardiac output; IABP = intraaortic balloon pump; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle; VA ECMO = venoarterial extracorporeal membrane oxygenation.

(IABP), Impella (Abiomed), TandemHeart (LivaNova), Centrimag (Thoratec), and venoarterial extracorporeal membrane oxygenation (VA ECMO). For patients with isolated right ventricular failure, options include Impella RP, Tandem Protek Duo (LivaNova), Centrimag, and VA ECMO. Biventricular failure can be supported with two independent devices or with VA ECMO. Of note, if cardiac dysfunction is accompanied by severe respiratory failure, VA ECMO, in which a pump is combined with a membrane oxygenator capable of oxygenation and decarboxylation of blood, is necessary.

In deciding which device is most appropriate, primary consideration is given to which ventricle is failing and how much additional blood flow is required to reverse the shock state. A summary of the devices, including ventricular support type and typical flow capabilities, is provided in Table 2.

CLINICAL OUTCOMES

Although MCS use has grown, randomized trials are limited and have not demonstrated improved survival. The IABP-SHOCK II (Intra-aortic Balloon Pump in Shock II) trial randomized patients with myocardial infarction with CS to IABP or medical therapy and did not find a 30-day mortality difference (3). The Impella and the TandemHeart have been compared with IABP in patients with CS after myocardial infarction, and despite improving cardiac output relative to the IABP, these devices have failed to demonstrate a mortality benefit (4, 5). A randomized trial evaluating the utility of VA ECMO in CS is planned (NCT02301819).

Despite the lack of trials demonstrating mortality benefit, studies support the efficacy of mechanical devices to reverse shock and bridge patients to recovery or to implantable devices (6, 7). Such improvements in hemodynamics likely fuel the continued use of these devices. As the technology continues to evolve, further studies will be needed to define the expanding role of these devices in the management of CS.

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DIRECT ORAL ANTICOAGULANTS

Megan Acho and Stephanie I. Maximous

Direct oral anticoagulants (DOACs) are increasingly used; thus, intensivists must be familiar with their mechanisms and pharmacology (Table 3) to better anticipate and manage potential complications. DOACs fall into one of two classes: *1*) direct thrombin inhibitors, which block thrombin (factor IIa), preventing fibrinogen's cleavage into fibrin and thus preventing clot formation, and *2*) factor Xa inhibitors, which block the conversion of prothrombin into thrombin. The latter are easily recognized by the suffix "-xaban" or "x-ban."

CONSIDERATIONS FOR DOAC USE IN THE INTENSIVE CARE UNIT

Risk of clinically significant bleeding is of paramount concern when selecting DOACs in the intensive care unit. Intensivists often defer initiating DOAC therapy during critical illness, relying instead on agents with short half-lives that may be rapidly discontinued. Although several clinical trials demonstrate reduced risk of bleeding

Table 3. Overview of direct oral anticoagulants

	Name	Indications	Delivery	Dose Adjustment or Avoidance Recommended for Renal Impairment?	Reversal	Other Considerations
Direct thrombin inhibitors	Bivalirudin	Periprocedural in patients undergoing angioplasty or percutaneous coronary intervention	Intravenous	Yes	Hemodialysis	Monitor with aPTT
	Argatroban	Periprocedural in patients undergoing percutaneous coronary intervention	Intravenous	No	None	None
		HIT				
		HITT				
	Dabigatran	VTE prophylaxis, treatment	Oral	Yes	Idarucizumab (monoclonal antibody fragment that binds dabigatran)	Not approved in patients with mechanical valves
		VTE prophylaxis after knee and hip replacement	Requires BID dosing		Hemodialysis	Ecarin-based assays correlate with drug concentration
		Atrial fibrillation/flutter	—		—	Interacts with inducers/inhibitors of P-glycoprotein
		—	—		—	Do not use in pregnancy
Factor Xa inhibitors	Apixaban	VTE prophylaxis, treatment	Oral	Yes	Andexanet alfa	Not approved in patients with mechanical valves
		Atrial fibrillation/flutter	Requires BID dosing			Not for use in pregnancy
	Rivaroxaban	VTE prophylaxis, treatment	Oral	Yes	Andexanet alfa	Not approved in patients with mechanical valves
		VTE prophylaxis after knee and hip replacement	Once-daily dosing			Limited data to suggest rivaroxaban may be used in patients with a BMI >40 kg/m^2
		Atrial fibrillation/flutter	—			Interacts with inducers/inhibitors of P-glycoprotein, CYP34A

Table 3. Overview of direct oral anticoagulants (continued)

Name	Indications	Delivery	Dose Adjustment or Avoidance Recommended for Renal Impairment?	Reversal	Other Considerations
	—	—	—		Not for use in pregnancy
Edoxaban	VTE prophylaxis, treatment (after initial parenteral treatment)	Oral	Yes	Andexanet alfa	Not approved in patients with mechanical valves
	Atrial fibrillation/flutter	Once-daily dosing			Not for use in pregnancy
Betrixaban	VTE prophylaxis	Oral	Yes	Andexanet alfa	Not approved in patients with mechanical valves
		Once-daily dosing			Not for use in pregnancy

Definition of abbreviations: aPPT = activated partial thromboplastin time; BID = twice daily; BMI = body mass index; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia and thrombosis; VTE = venous thromboembolism.

with certain DOACs relative to warfarin (1–3), DOAC use may still be complicated by life-threatening bleeding and studies have not been done on critically ill patients (4).

Before initiating a DOAC, drug- and patient-related factors must be considered. DOACs require dose adjustments in patients with kidney disease and should be avoided in those with significant renal dysfunction. Prior history of major bleeding, concurrent use of antiplatelet therapy, thrombocytopenia, and coagulation factor deficiency increase bleeding risk. In patients with planned invasive procedures, DOACs should be stopped if there is a high risk of bleeding (5).

Minor bleeding does not necessarily require interruption of DOACs, as withdrawal of the anticoagulant therapy may result in increased risk of thrombotic complications. In these cases, the patient should be monitored, and local interventions to manage bleeding can be pursued. The inability to assess drug levels and degree of anticoagulation to guide anticoagulant reversal complicates management decisions.

MANAGEMENT OF BLEEDING IN PATIENTS ON DOACS

In cases of serious bleeding (i.e., intracerebral hemorrhage, compartment syndrome) and bleeding that requires transfusion or invasive intervention, DOACs should be discontinued and reversal of the anticoagulated state attempted. Reversal strategies may include dialysis for dabigatran removal, administration of clotting factor products such as activated prothrombin complex concentrate (PCC) or unactivated 4 factor PCC, or administration of agent-specific reversal drugs. Idarucizumab may be used to reverse the effects of dabigatran if conservative measures are ineffective in a life-threatening

bleed or if an emergency procedure is required and thrombin time is prolonged (6). When idarucizumab is not available, PCC should be used. For severe life-threatening bleeding with factor Xa inhibitors, particularly intracerebral hemorrhage, andexanet alfa may be used (7). This medication is not readily available at most centers and cost remains prohibitive. More commonly, 4 factor PCC is administered. Both andexanet alfa and PCC increase risk of thrombosis and should only be given for significant bleeding events.

There is no high-quality evidence to endorse a particular drug reversal strategy. The risk of thrombosis in the setting of DOAC reversal must be weighed against the risk of morbidity from the bleeding event. Similarly, there is no universally endorsed guideline for transition from DOACs to continuous heparin infusions. More data are needed to guide the complex management of critically ill patients on DOACs.

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UPPER GASTROINTESTINAL HEMORRHAGE

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INITIAL APPROACH

The initial approach to undifferentiated upper gastrointestinal hemorrhage (UGIH) requires simultaneous diagnostic testing, hemodynamic assessment, and resuscitation.

Bedside evaluation focuses on the identification of shock and the source of bleeding. Bright red blood per rectum with hemodynamic instability is assumed to be due to massive UGIH. Clinical evaluation should include iterative assessment of hemodynamics and laboratory testing for anemia, coagulopathy, end-organ injury, and markers of cirrhosis. Endotracheal intubation for airway protection may be necessary in cases of

active hematemesis, severe shock, or encephalopathy.

Resuscitation requires robust vascular access such as two short 18-gauge or larger catheters in proximal veins or a resuscitation catheter in a central vein (1). Conventional triple lumen and peripherally inserted central catheters have increased resistance to flow owing to length and relatively narrow diameter, making them less ideal for rapid infusion. While awaiting crossmatched blood products, crystalloids or uncrossmatched packed red blood cells (PRBCs) may be used. In massive hemorrhage, transfusion is guided by hemodynamics and blood loss, not laboratory values. Although practices vary across institutions, data extrapolated from traumatology support administering a ratio of 1 unit PRBCs: 1 unit platelets: 1 unit fresh frozen plasma to minimize coagulopathy (2). Once relative hemodynamic stability is achieved, PRBC transfusion should follow a restrictive transfusion threshold of <7 g/dl, which reduces mortality and rebleeding rates, particularly in patients with cirrhosis (1). Usual practice is to correct thrombocytopenia if platelets are $<50 \times 10^9$/L. Coagulopathy due to vitamin K antagonists should be reversed. Prothrombin complex concentrate may be preferable to fresh frozen plasma owing to lower volume and faster time of onset, higher cost notwithstanding (3).

Adjunctive initial therapy often includes a proton pump inhibitor (PPI) and octreotide, as these therapies have potential benefits without significant adverse effects. Figure 3 summarizes the management of upper gastrointestinal hemorrhage.

DIFFERENTIATION OF UGIH

Timely endoscopy frequently enables diagnosis and control of UGIH. Consensus statements advocate endoscopy within 24 hours for hospitalized patients (1). In a recent study in patients with UGIH at high risk for further bleeding or death, endoscopy performed <6 hours after gastrointestinal consultation did not result in lower 30-day mortality than endoscopy performed between 6 and 24 hours after consultation (4). Achieving hemodynamic stability to tolerate sedation during endoscopy is important but does not preclude endoscopy in a hemodynamically tenuous patient requiring ongoing resuscitation.

If endoscopy is unavailable or delayed, gastric lavage and computed tomography angiography can be used to attempt to localize the source of bleeding. Gastric tube aspiration has a high false-negative rate. Computed tomography angiography is highly sensitive for detecting rapid gastrointestinal bleeding (5).

DIFFERENTIATED UGIH

Peptic ulcers are the most common etiology of UGIH and are treated with high-dose PPI to reduce the risk of rebleeding and need for endoscopic intervention. They do not have an effect on mortality (6). PPI therapy may provide hemostasis in other causes of UGIH owing to clot stabilization. Other sources of UGIH such as mucosal/erosive disease, Mallory-Weiss tear, and malignancy require an individualized approach coordinated with a gastroenterologist and surgeon.

In variceal UGIH, octreotide has been shown to help achieve hemostasis and prevent rebleeding but does not have an established mortality benefit (7). Octreotide decreases the hepatic venous pressure gradient and splanchnic vasodilation. Approximately 20% of patients with variceal UGIH have an active infection; thus, investigation for source and empiric antibiotics are recommended regardless of whether a patient has ascites
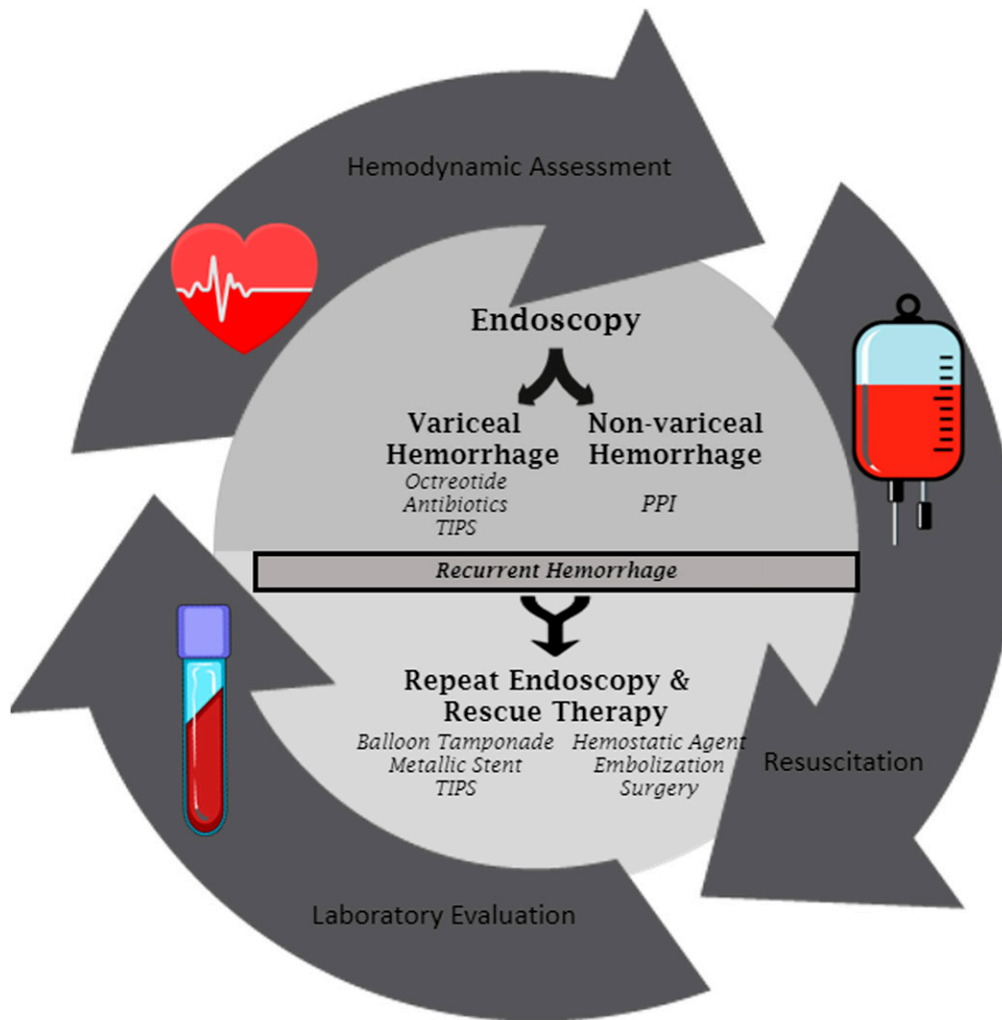
Figure 3. Management of upper gastrointestinal hemorrhage. Continuous hemodynamic evaluation, resuscitation, and laboratory assessment are critical while definitive therapy is organized. PPI = proton pump inhibitor; TIPS = transjugular intrahepatic portosystemic shunt.

(1–8). Antibiotics decrease the rate of bacterial infection and incidence of rebleeding and improve survival (9). Antibiotic choice is typically a third-generation cephalosporin or fluoroquinolone for a maximum of 7 days. PPI is not indicated in variceal UGIH unless peptic ulcer disease is present. β-Blockers should be withheld.

RESCUE THERAPIES

In recurrent UGIH, second-look endoscopy is indicated to reattempt source identification and control. Endoscopically administered spray hemostatic agents are increasingly deployed as a temporizing measure in nonvariceal UGIH. If hemorrhage cannot be controlled, interventional radiology can often perform superselective embolization given high surgical morbidity. Surgical intervention remains an available therapy in select cases.

In variceal UGIH, bleeding cannot be controlled or recurs in 20% of patients. Balloon tamponade devices and transjugular intrahepatic portosystemic shunt (TIPS) are rescue therapies. Balloon tamponade devices provide immediate control in >80% of patients,

but use is limited to 24 hours because of the risk of esophageal necrosis (10). TIPS is highly effective in variceal UGIH. After successful endoscopy for UGIH, TIPS within 72 hours of admission is associated with lower treatment failure and mortality in selected high-risk patients (11).

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VASOPRESSOR SELECTION

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OVERVIEW

Vasopressor medications are a cornerstone of treatment in shock. They are indicated when tissue perfusion remains insufficient despite adequate intravascular volume resuscitation. Vasopressors restore tissue perfusion predominantly through vasoconstriction, although many also increase cardiac contractility (Table 4). Despite their longstanding and widespread use in critical care, data supporting the use of a single vasopressor over another remain limited.

Table 4. Commonly used vasoactive medications and their receptor activity, physiologic effects, and relevant clinical information

Vasoactive	Receptor Activity	CO	SVR	Indications	Adverse Effects	Usual Dose Range
Phenylephrine	α_1	↔	↑↑	Alternative to β_1 agonists	Reflex bradycardia	0.5–6 mcg/kg/min
Norepinephrine	$\alpha_1 > \beta_1$	↔/↑	↑↑	Septic shock, cardiogenic shock	Tachyarrhythmias	0.025–0.3 mcg/kg/min
Epinephrine	$\alpha_1 = \beta_1 > \beta_2$	↑↑	↑/↓	Anaphylactic shock, bradycardia, cardiogenic shock	Tachyarrhythmias, splanchnic vasoconstriction	0.01–0.7 mcg/kg/min
Dopamine	—	—	—	Relative or absolute bradycardia and low risk for tachyarrhythmias	High rate of tachyarrhythmias	2–20 mcg/kg/min
Low	$DA > \beta_1$	↑	↔			
Medium	$DA = \beta_1 > \alpha_1$	↑	↑			
High	$\beta_1 > DA = \alpha_1$	↑	↑↑			
Dobutamine	$\beta_1 > \beta_2$	↑	↓	Cardiogenic shock	Tachyarrhythmias, hypotension	2–20 mcg/kg/min
Vasopressin	V_{12}	↔	↑	Second line for septic shock, may reduce atrial fibrillation	Mesenteric ischemia at higher doses	0.01–0.07 mcg/kg/min
Angiotensin II	AT_1	↔	↑	Refractory septic shock	Thrombosis	10–40 ng/kg/min
Methylene blue	Inhibits NOS and sGC	↔	↑	Refractory vasoplegia	Hemolysis, serotonin syndrome	1.5–2 mg/kg over 20–60 min

Definition of abbreviations: α_1 = alpha-1 receptor; AT_1 = angiotensin II receptor type 1; β_1 = beta-1 receptor; β_2 = beta-2 receptor; CO = cardiac output; DA = dopamine receptor; NOS = nitric oxide synthase; sGC = soluble guanylate cyclase; SVR = systemic vascular resistance, V_2 = vasopressin receptor 2.

CATECHOLAMINES

Catecholamines are the most common vasopressor and inotropic agents used in the treatment of shock. Historically, both dopamine and norepinephrine were recommended as first-line agents. In 2010, the SOAP II (Sepsis Occurrence in Acutely Ill Patients) trial was published comparing dopamine and norepinephrine in 1,679 patients with shock. There was no mortality difference between groups, but dopamine was associated with increased adverse events, primarily arrhythmias. Subgroup analysis of patients with cardiogenic shock showed increased mortality in the dopamine group (1). A subsequent meta-analysis of 11 studies comparing dopamine with norepinephrine in septic shock found dopamine to be associated with increased mortality and arrhythmias (2). Data on the use of phenylephrine in septic shock and clinical outcomes are limited, although small studies have suggested similar performance when compared with norepinephrine (3). Epinephrine is most often used in the treatment of anaphylactic shock. It has similar hemodynamic effects to norepinephrine but results in transient lactic acidosis and a higher rate of arrhythmias (4). Based on the available data and expert opinion, norepinephrine is considered the first-line vasopressor for the management of septic shock (5). This is supported by observational data from a 2011 U.S. norepinephrine shortage that revealed an increase in septic shock mortality in affected hospitals, with phenylephrine and dopamine being the most commonly used alternative

vasopressors (6). In cardiogenic shock, the use of agents with greater inotropic properties, such as dobutamine, is often required.

VASOPRESSIN

Vasopressin is commonly used as a second-line agent in the treatment of vasodilatory shock. The VASST (Vasopressin and Septic Shock Trial) trial compared norepinephrine alone with norepinephrine plus vasopressin in 778 patients with septic shock and found no difference in mortality (7). In the VANISH (Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease) study, a comparison of norepinephrine plus hydrocortisone or placebo and vasopressin plus hydrocortisone or placebo, there was no difference in kidney failure–free days or mortality (8). The use of vasopressin is recommended as an additional agent in refractory vasodilatory shock or with the intent of reducing the dose of catecholamine used (5). The latter use is supported by meta-analysis data

demonstrating lower rates of atrial fibrillation when vasopressin was used with catecholamine vasopressors compared with catecholamines alone (9).

ANGIOTENSIN II

Angiotensin II has emerged as a novel noncatecholamine vasopressor for treatment of vasodilatory shock. The ATHOS-3 (Angiotensin II for the Treatment of High-Output Shock) trial, a randomized controlled clinical trial including patients with vasodilatory shock receiving high-dose norepinephrine, demonstrated that angiotensin II was effective at increasing mean arterial pressure and was well tolerated when compared with placebo (10). Angiotensin II is a promising third-line vasopressor after norepinephrine and vasopressin, as all three agents have differing mechanisms of action, although further study is needed before widespread adoption.

Author disclosures are available with the text of this article at www.atsjournals.org.

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