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for guiding interventions or improving outcomes in sepsis is unproven. The pathogenesis of coagulation abnormalities in sepsis, as discussed above, is attributed to activation of innate immune cellular and soluble responses including cytokines, chemokines, and complement; endo thelial activation and injury; platelet activation and aggregation; and clotting cascade induction, suppression of antithrombotic molecules, and activation of antifibrinolytic molecules. This procoagulant milieu results in platelet and clotting factor consumption, which paradoxically increases bleeding risk. Current recommendations for DIC manage ment focus on mitigating bleeding risk. Recommendations include administration of cryoprecipitate to patients with fibrinogen <150 mg/ dL; administration of fresh frozen plasma to patients with prolongated PT/INR and evidence of bleeding; and administration of platelets to patients with platelet counts ≤50 × 109/L and evidence of bleeding. Platelet transfusion thresholds are lower in patients at increased bleed ing risk including patients undergoing chemotherapy, post–hemopoietic stem cell transplantation patients, and postsurgical patients. Venous thromboembolism prophylaxis, with low-molecular-weight heparin preferred over unfractionated heparin, is recommended in patients with sepsis or septic shock. Full-dose anticoagulation is not recom mended for prophylactic use in septic patients, but instead is reserved for standard treatment indications including deep-venous thrombosis and pulmonary embolism.

PART 8 Critical Care Medicine Anemia is common in septic patients, and transfusion of packed red blood cells to maintain hemoglobin >7.0 g/dL is recommended. How ever, a more conservative, higher hemoglobin target may be appropri ate in some patients based on individual factors including degree of hypoxemia, myocardial ischemia, and active hemorrhage. ■ ■HOST-TARGETED THERAPIES Despite years of effort and many promising preclinical studies, there are currently no U.S. Food and Drug Administration–approved therapies targeting pathologic immune responses during bacterial sepsis. Failed therapeutic targets include proinflammatory media tors (e.g., anti-TNF, anti-IL-1, anti-TLR-4, anti-C5a), components of the coagulation cascade (e.g., antithrombin III, activated protein C, thrombomodulin), and many others. Other adjunctive therapies that have been evaluated include polymyxin-B hemoperfusion, intravenous immunoglobulin, and vitamin C, all determined to be not beneficial. Future work aimed at developing host-targeted sepsis therapies will require a deeper understanding of cellular and

soluble mediators contributing to its pathogenesis in blood and tissues and how these mediators vary across host, pathogen, and timing of infection. Emerg ing technologies including single-cell transcriptomics, proteomics, metabolomics, and spatial-transcriptomics should aid in identifying novel therapeutic targets, and innovative, adaptive clinical trial designs will help stratify heterogeneous septic patients into likely responders to specific therapies. DEESCALATING CARE AND LIMITING LONG-TERM SEQUALAE In sepsis survivors who remain hospitalized, care should focus on limiting complications and optimizing long-term outcomes. Indwell ing central venous and urinary catheters should be removed when no longer needed. Early mobilization, deep-venous thrombosis preven tion, discontinuing unnecessary intravenous fluids, and judicious use of diuretics in patients with significant fluid overload are all important interventions. Many sepsis survivors experience long-term compli cations including physical, cognitive, and psychological sequelae. Physical sequelae include prolonged fatigue, muscle loss, weakness, and diminished functional capacity. Cognitive and psychological sequelae include cognitive decline, dementia, depression, and decreased quality of life. Sepsis survivors have increased risk of cardiovascular events, including myocardial infarction and stroke, recurrent infection, read mission, and death. Fifty percent of initial sepsis survivors are rehos pitalized within 1 year, and one in six die within the first year. Most deaths following sepsis occur in the first 6 months, but the risk of death remains elevated for up to 2 years. Common causes of readmis sion include heart failure, myocardial infarction, pneumonia, chronic

obstructive pulmonary disease, and urinary tract infections. Given the high prevalence of long-term sequelae and complications among sepsis survivors, the 2021 Surviving Sepsis Campaign Guidelines recommend that hospital discharge plans include screening for economic and social support and establishing follow-up with providers who can assess and support physical, cognitive, and psychological issues. ■ ■FURTHER READING Baghela A et al: Predicting sepsis severity at first clinical presentation: The role of endotypes and mechanistic signatures. EBioMedicine 75:103776, 2022. Evans L et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Crit Care Med 49:e1063, 2021. Habimana R et al: Sepsis-induced cardiac dysfunction: A review of pathophysiology. Acute Crit Care 35:57, 2020. Raia L, Zafrani L: Endothelial activation and microcirculatory disor ders in sepsis. Front Med (Lausanne) 9:907992, 2022. Rhee C et al: Incidence and trends of sepsis in US hospitals using clini cal vs claims data, 2009-2014. JAMA 318:1241, 2017. Rhee C et al: Prevalence of antibiotic-resistant pathogens in cultureproven sepsis and outcomes associated with inadequate and broadspectrum empiric antibiotic use. JAMA Netw Open 3:e202899, 2020. Singer M et al: The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315:801, 2016. Strich JR et al: Considerations for empiric antimicrobial therapy in sepsis and septic shock in an era of antimicrobial resistance. J Infect Dis 222:S119, 2020. Wiersinga WJ, van der Poll T: Immunopathophysiology of human sepsis. EBioMedicine 86:104363, 2022. Zarbock A et al: Sepsis-associated acute kidney injury: Consensus report of the 28th Acute Disease Quality Initiative workgroup. Nat Rev Nephrol 19:401, 2023. David H. Ingbar, Holger Thiele

Cardiogenic Shock and Pulmonary Edema Cardiogenic shock and pulmonary edema are each life-threatening high-acuity conditions that require treatment as medical emergen cies, usually in an intensive care unit (ICU) or cardiac intensive care unit (CICU). The most common joint etiology is severe left ventricu lar (LV) dysfunction from myocardial infarction (MI) that leads to pulmonary congestion and/or systemic hypoperfusion (Fig. 316-1). The pathophysiologies of pulmonary edema

and shock are discussed in Chaps. 39 and 314, respectively. CARDIOGENIC SHOCK Cardiogenic shock (CS) is a low cardiac output state resulting in life-threatening end-organ hypoperfusion and hypoxia. The clini cal presentation is typically characterized by persistent hypotension (<90 mmHg systolic blood pressure [BP]) or <60–65 mmHg mean arterial pressure that is unresponsive to volume replacement and/or requires use of vasopressors to maintain adequate BP) and is accompa nied by clinical features of peripheral hypoperfusion, such as elevated arterial lactate (>2 mmol/L). Objective hemodynamic parameters such as cardiac index or pulmonary capillary wedge pressure can help confirm a cardiogenic cause of shock but are not mandatory. The inhospital mortality rates range from 40 to 60%, depending on shock severity and the associated underlying cause. The Society for Cardio vascular Angiography and Interventions (SCAI) classification of CS

Ventilation Fluids inotropes/ vasopressors SIRS + + Mechanical support device + eNOS iNOS Peripheral perfusion ↓ Bleeding/ transfusion + Reperfusion: PCI/CABG Vasoconstriction Fluid retention NO ↑ Peroxynitrite ↑ Interleukins ↑ TNF-α ↑ SVR ↓ Pro-inflammation Catecholamine sensitivity ↓ Contractility ↓ FIGURE 316-1 Pathophysiology of cardiogenic shock and potential treatment targets. The pathophysiologic concept of the expanded cardiogenic shock spiral and treatment targets. CABG, coronary artery bypass grafting; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; LVEDP, left ventricular end-diastolic pressure; NO, nitric oxide; PCI, percutaneous coronary intervention; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; TNF, tumor necrosis factor. (Reproduced with permission from H Thiele et al: Shock in acute myocardial infarction: The Cape Horn for trials? Eur Heat J 31:1828, 2010.) that was introduced in 2019 includes five categories: (A) at risk, (B) beginning or preshock, (C) classical, (D) deteriorating, and (E) extre mis CS (Fig. 316-2). Preshock is defined as clinical evidence of relative hypotension or tachycardia without hypoperfusion. These patients should be monitored closely and treated early to avoid development of classical CS. Extremis CS includes cases in which considerations about futility of treatment should be done and possibly palliative care initiated. The SCAI definition recently was updated based on several validation studies; it still includes the stages A–E but also includes a three-axis model based on (1) shock severity, (2) phenotype and etiol ogy, and (3) risk modifiers such as cardiac arrest. Although declining in incidence, acute MI with LV dysfunction remains the most frequent cause of CS, with other causes listed in Table 316-1. Circulatory failure based on cardiac dysfunction may be caused by primary myocardial failure, most commonly secondary to acute MI (Chap. 286), and less frequently by acute or chronic heart failure as a cause of cardiomyopathy or myocarditis (Chaps. 266–270), cardiac tamponade (Chap. 281), arrhythmias (Chap. 261), or critical valvular heart disease (Chap. 262). Incidence The incidence of CS complicating acute MI has decreased to 5–10%, largely due to increasing use of early mechanical reperfusion therapy for acute MI. Shock is more common with ST-segment eleva tion MI (STEMI) than with non-STEMI (Chap. 286). LV failure accounts for ~80% of cases of CS complicating acute MI. Acute severe mitral regurgitation (MR), ventricular septal rupture (VSR), predominant right ventricular (RV) failure, and free wall rup ture or tamponade account for the remainder. A recently recognized uncommon cause of transient CS is the Takotsubo syndrome. Pathophysiology The understanding of the complex pathophysi ology of CS has evolved over the past decades. In general, a profound

Acute Myocardial Infarction Left ventricular dysfunction systolic diastolic LVEDP ↑ Lung edema ↑ Cardiac output ↓ Stroke volume ↓ Hypoxia Hypotension Coronary perfusion ↓ CHAPTER 316 Ischemia Cardiogenic Shock and Pulmonary Edema Progressive left ventricular dysfunction Death

depression of myocardial contractility results in a deleterious spiral of reduced cardiac output, low BP, and ongoing myocardial ischemia, fol lowed by further contractility reduction (Fig. 316-1). This vicious cycle usually leads to death if not interrupted. CS can result in both acute and subacute derangements to the entire circulatory system. Hypo perfusion of vital organs and extremities remains a clinical hallmark. Although ineffective stroke volume is the inciting event, inadequate circulatory compensation also may contribute to shock. Initial periph eral vasoconstriction may improve coronary and peripheral perfusion at the cost of increased afterload, potentially worsening ischemia. However, over the course of CS, the systemic inflammation response triggered by acute cardiac injury often induces pathologic vasodilata tion. Inflammatory cytokines and inducible (as well as endothelial) nitric oxide (NO) synthase may augment production of NO and its by-product, peroxynitrite, which has a negative inotropic effect and is cardiotoxic. Lactic acidosis and hypoxemia contribute to the vicious circle, as severe acidosis reduces the efficacy of endogenous and exog enous catecholamines. During ICU or CICU support, bleeding and/or transfusions may trigger inflammation and are usually associated with higher mortality (Fig. 316-1). Patient Profile In patients with MI, older age, prior MI, diabetes mellitus, anterior MI location, and multivessel coronary artery dis ease with extensive coronary artery stenoses are associated with an increased risk of CS. Shock associated with a first inferior MI should prompt a search for a mechanical cause or RV involvement. CS may rarely occur in the absence of significant coronary stenosis, as seen in Takotsubo syndrome or fulminant myocarditis. Timing Shock is present on admission in approximately onequarter of MI patients who develop CS; of the remaining patients, one-quarter develop it rapidly thereafter, within 6 h of MI onset, and

Stage E: Extremis CS. Patients experiencing cardiac arrest with ongoing cardiopulmonary resuscitation (CPR) and/or ECMO. E Extremis D Deteriorating C Classical cardiogenic shock B Beginning cardiogenic shock PART 8 Critical Care Medicine A At risk for cardiogenic shock development FIGURE 316-2 Shock severity definition. Five categories of cardiogenic shock (CS). Stage A: At risk: Patients “at risk” for cardiogenic shock development but not currently experiencing signs/symptoms of cardiogenic shock. Stage B: Patients with clinical evidence of relative hypotension or tachycardia without hypoperfusion being at “beginning” of cardiogenic shock. Stage C: Patients in the state of “classic” cardiogenic shock. Stage D: Cardiogenic shock signals deteriorating or “doom.” Stage E: Patients in “extremis,” such as those experiencing cardiac arrest with ongoing cardiopulmonary resuscitation and/or extracorporeal membrane oxygenation (ECMO) cardiopulmonary resuscitation. MCS, mechanical circulatory support. (Reproduced with permission from H Thiele et al: Management of cardiogenic shock complicating myocardial infarction: An update 2019. Eur Heart J 40:2671, 2019.) another quarter develop shock later on the first day. Later onset of CS may be due to reinfarction, marked infarct expansion, or mechanical complications. Diagnosis For these unstable patients, supportive therapy must be initiated simultaneously with diagnostic evaluation (Fig. 316-3). A focused history and physical examination should be performed along with an electrocardiogram (ECG), chest x-ray, arterial blood gas (ABG) analysis, lactate measurement, and blood specimens for laboratory analysis. Initial echocardiography is an invaluable tool to elucidate the underlying cause of CS and also assess if it is predominantly left, right, or biventricular in origin. CLINICAL FINDINGS Most patients initially are dyspneic, pale, appre hensive, and diaphoretic, and mental status may be altered. The pulse is typically weak and rapid, or occasionally, severe bradycardia due to highgrade heart block may be present. Systolic BP is typically reduced (<90 mmHg, or catecholamines are required to maintain BP >90 mmHg), but occasionally, BP may be maintained by very high systemic vascular resistance.

Tachypnea and jugular venous distention may be present. Typically, there is a weak apical pulse and a soft S1, and an S3 gallop may be audible. Acute, severe MR and VSR usually are associated with char acteristic systolic murmurs (Chap. 286). Crackles are audible in most patients with LV failure. Oliguria/anuria is common. CS patients often require early mechanical ventilation (~80%) for management of acute hypoxemia, increased work of breathing, and hemodynamic instability; vasopressors often are required to maintain adequate BP. LABORATORY FINDINGS The white blood cell count and C-reactive protein typically are elevated. Renal function often is progressively impaired. Newer renal function markers such as cystatin C or neu trophil gelatinase–associated lipocalin (NGAL) do not add prognostic information over creatinine. Hepatic transaminases are elevated due to liver hypoperfusion in ~20% of patients, which is a marker of high mortality. By definition, in SCAI shock criteria, the arterial lactate level is elevated to >2 mmol/L; if higher, prognosis is worse, and those with lactate >8 mmol/L are in SCAI stage E. ABGs usually demon strate hypoxemia and an anion gap metabolic acidosis. Glucose levels at admission are often elevated, a strong independent predictor for mortality. Cardiac markers, creatine kinase and its MB fraction, and troponins I and T are typically markedly elevated in acute MI.

Stage D: CS signals deteriorating or doom. Similar to stage C but getting worse and failing to respond to initial interventions. Stage C: Classic CS. Manifest CS with hypoperfusion requiring intervention (inotropes, vasopressors, or MCS, excluding ECMO) beyond volume resuscitation to restore perfusion. Stage B: Clinical evidence of relative hypotension or tachycardia without hypoperfusion being at “beginning” of CS (preshock). Stage A: Currently no signs/symptoms of CS, but being “at risk” for its development. ELECTROCARDIOGRAM In acute MI with CS, Q waves and/or ST ele vation in multiple leads or left bundle branch block are usually present. Approximately one-half of MIs with CS are anterior infarctions. Global ischemia due to severe left main stenosis usually is accompanied by ST-segment elevation in lead aVR and ST depressions in multiple leads. CHEST ROENTGENOGRAM The chest x-ray typically shows pulmo nary vascular congestion and often pulmonary edema but may be normal in up to a third of patients. The heart size is usually normal when CS results from a first MI but may be enlarged when it occurs in a patient with a previous MI. ECHOCARDIOGRAM An echocardiogram (Chap. 248) should be obtained promptly in patients with suspected/confirmed CS to help define its etiology. Echocardiography is able to delineate the extent of infarction/myocardium in jeopardy and the presence of mechanical complications such as VSR, MR, or cardiac tamponade. Furthermore, RV impairment, valvular obstruction or insufficiency, dynamic LV outflow tract obstruction, and proximal aortic dissection with aortic regurgitation or tamponade may be seen, or indirect evidence for pul monary embolism may be obtained (Chap. 290) (Table 316-2). PULMONARY ARTERY CATHETERIZATION The use of pulmonary artery catheter (PAC) hemodynamic monitoring had declined until recently because clinical trials have shown no mortality benefit. The recent increase in PAC use arose because hemodynamic data and waveforms can be helpful in both diagnosis and management. Recent observational data suggest better outcome with PAC use applied in this way. PAC hemodynamic data can confirm the presence and severity of CS, involvement of the right ventricle, left-to-right shunting, pulmo nary artery pressures and transpulmonary gradient, and pulmonary and systemic vascular resistance. It can help in recognition of acute MR, decreased left atrial filling pressure, right or left dominance, and secondary septic causes and also can exclude left-to-right shunts. Equalization of diastolic pressures suggests cardiac tamponade, but echocardiogram is more definitive. The detailed hemodynamic pro file can be used to individualize and monitor therapy and to provide prognostic information, such as cardiac index and cardiac power. The use of a PAC is currently recommended

by the American Heart Asso ciation for potential utilization in cases of diagnostic or CS manage ment uncertainty or in patients with severe CS who are unresponsive

TABLE 316-1 Etiologies of Cardiogenic Shocka and Cardiogenic Pulmonary Edema Etiologies of Cardiogenic Shock or Pulmonary Edema Acute myocardial infarction/ischemia Left ventricular failure Ventricular septal rupture Papillary muscle/chordal rupture–severe mitral regurgitation Ventricular free wall rupture Other conditions complicating large myocardial infarctions Excess negative inotropic or vasodilator medications Post–cardiac arrest Postcardiotomy Refractory sustained supraventricular or ventricular tachyarrhythmias Refractory sustained bradyarrhythmias Acute fulminant myocarditis End-stage cardiomyopathy Takotsubo syndrome/apical ballooning syndrome Hypertrophic cardiomyopathy with severe outflow obstruction Aortic dissection with aortic insufficiency or tamponade Severe valvular heart disease Critical aortic or mitral stenosis Acute severe aortic regurgitation or mitral regurgitation Toxic/metabolic β Blocker or calcium channel antagonist overdose Pheochromocytoma Scorpion venom Hypertensive crisis Post–cardiac arrest stunning Myocardial depression in setting of septic shock or systemic inflammatory response syndrome Myocardial contusion Other Etiologies of Cardiogenic Shockb Right ventricular failure due to: Acute myocardial infarction Acute or decompensated chronic cor pulmonale Pericardial tamponade Toxic/metabolic Severe acidosis, severe hypoxemia aThe etiologies of cardiogenic shock are listed. Most of these can cause pulmonary edema instead of shock or pulmonary edema with cardiogenic shock. bThese cause cardiogenic shock but not pulmonary edema. to initial therapy. PAC use also can help differentiate noncardiogenic pulmonary edema. ADVANCED HEMODYNAMIC MONITORING Recently, new central venous catheter systems linked to computer-based algorithms provide continuous monitoring of a variety of derived hemodynamic param eters, including cardiac output, stroke volume, stroke volume variation, and systemic vascular resistance (Table 316-3). When combined with a femoral arterial catheter, calculated extravascular lung water and pulmonary permeability index can be monitored. The information allows for more rational therapy and assessment but has not yet shown improved clinical outcomes in patients with shock or pulmonary edema. CARDIAC CATHETERIZATION AND CORONARY ANGIOGRAPHY The definition of the coronary anatomy provides useful information and is immediately indicated in all patients with CS complicating MI for further reperfusion treatment. Furthermore, cardiac catheteriza tion should also be considered for resuscitated cardiac arrest sur vivors without ST-segment elevation in CS because ~70% of these patients have relevant coronary artery disease. However, routine early invasive coronary angiography did not show a survival benefit in

hemodynamically stable patients after resuscitation from cardiac arrest without ST-segment elevation in two recent large, randomized trials. Consequently, guidelines were revised to avoid routine immediate cardiac catheterization in these patients.

TREATMENT Acute Myocardial Infarction GENERAL MEASURES In addition to the usual treatment of acute MI (Chap. 286), initial therapy is aimed at maintaining adequate systemic and coronary perfusion by raising the BP with vasopressors and adjusting vol ume status to a level that ensures optimum LV filling pressure (Fig. 316-3). There is some interpatient variability, but generally, adequate perfusion occurs with a mean arterial BP of 60–65 mmHg or a systolic BP of ~90 mmHg. Hypoxemia and acidosis need to be corrected, particularly since acidemia attenuates vasoconstriction by catecholamines. Up to 90% of patients require ventilatory sup port, decreasing the stress from increased work of breathing (see “Pulmonary Edema,” below) (Fig. 316-3).

Moderate glucose control (≤180 mg/dL or 10.0 mmol/L) should be a goal, and hypoglycemia must be avoided. Negative ionotropic agents should be discontin ued. Bradyarrhythmias may require transvenous pacing. Recur rent ventricular tachycardia or rapid atrial fibrillation may require immediate treatment (Chap. 253). REPERFUSION-REVASCULARIZATION Rapid revascularization of the infarct-related artery is the only evidence-based treatment strategy for mortality reduction in CS and forms the mainstay therapeutic intervention for CS due to MI (Fig. 316-2). In the SHOCK trial, 132 lives were saved per 1000 patients treated with early revascularization with percutaneous cor onary intervention (PCI) or coronary artery bypass graft (CABG) compared with initial medical therapy. Outcome benefit correlates strongly with the time between symptom onset, first medical con tact, and reperfusion. In general, PCI with drug-eluting stents of the infarct-related artery is the preferred reperfusion strategy. Approxi mately 80% of CS patients present with multivessel coronary artery disease. In these patients, culprit-only PCI with possible staged revascularization is the method of choice because it reduces mortal ity and requirement for renal replacement therapy at 30 days and 1 year in comparison to immediate multivessel PCI, as shown in the CULPRIT-SHOCK trial. The major driver for the reduction in the composite endpoint was a reduction in 30-day mortality. Updated recent clinical practice guidelines recommend avoiding immediate nonculprit PCI. Currently, vascular access for diagnostic angiogra phy and PCI via the radial artery are preferred when feasible over femoral arterial access due to the greater safety of radial artery access. CABG is currently performed in only 5% of cases, mainly if coronary anatomy is not amenable to PCI. VASOPRESSORS AND INOTROPES Inotropic agents are theoretically appealing in CS treatment. How ever, current evidence is scarce. Vasoactive medications often are used in the management of patients with CS, and all have important disadvantages, including increases in myocardial oxygen consump tion, afterload, lethal arrhythmias, and possible myocardial cell death. As a consequence, catecholamines should be used in the lowest possible doses for the shortest possible time. Despite their frequent use, little clinical outcome data prove their benefit or are available to guide the initial selection of vasoactive therapies in patients with CS. No vasopressor has been demonstrated to change outcome in large clinical trials. Norepinephrine is reasonable as the first-line vasopressor based on randomized trials compared to dopamine and also epinephrine. Norepinephrine was associated with fewer adverse events, including arrhythmias, compared to dopamine in a randomized trial of patients with several etiologies of circulatory shock and with improved survival in a prespecified subgroup of CS patients. Norepinephrine dosing is usually begun at CHAPTER 316 Cardiogenic Shock and Pulmonary Edema

Cardiogenic shock complicating infarction (STEMI or NSTEMI) Emergency invasive angiography (IB) Immediate echocardiography (IC) Left ventricular dysfunction (~80%) Cause of cardiogenic shock Right ventricular dysfunction (~7%) Mechanical complication (~13%) Catheterization laboratory/ OR Mechanical circulatory support Emergency PCI of culprit lesion (IB) Emergency CABG (if not amenable to PCI) (IB) No routine PCI of non-IRA lesions (IIIB) Fluid challenge as first-line therapy if no sign of overt fluid overload (IC) General measures: Mean blood pressure goal 65 mmHg, optimal end-organ perfusion, lactate clearance Invasive blood pressure monitoring (IC) PART 8 Critical Care Medicine Pulmonary artery catheter (IIB/C) Ventilatory support/O2 according to blood gases (IC) Intravenous inotropes to increase cardiac output (IIB/C) Vasopressors (norepinephrine preferable over dopamine) in presence of persistent hypotension (IIB/B) Ultrafiltration in refactory congestion not responding to diuretics (IIB/C) No routine IABP (IIIB) Yes Weaning Short-term percutaneous MCS in selected patients/refractory cardiogenic shock (IIB/C) Recovery of cardiac function? Yes Weaning Yes FIGURE 316-3 Emergency management of patients with cardiogenic shock (CS) complicating

acute myocardial infarction (AMI). Treatment algorithm for patients with CS. The class of recommendation and level of evidence according to European Society of Cardiology guidelines are provided (see “Further Reading”). CABG, coronary artery bypass grafting; ECG, electrocardiogram; IABP, intraaortic balloon pump; IRA, infarct-related artery; MCS, mechanical circulatory support; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; VSD, ventricular septal defect. (Reproduced with permission from H Thiele et al: Management of cardiogenic shock complicating myocardial infarction: An update 2019. Eur Heart J 40:2671, 2019.) 2–4 μg/min and titrated upward based on BP. Norepinephrine was associated with lower lactate levels and less refractory CS compared to epinephrine. Dopamine’s hemodynamic effects vary depend ing on dose, and there is interpatient variability in responses. Low doses stimulate renal dopaminergic receptors, and with increasing doses, there is stimulation of first β-adrenergic receptors and then α-adrenergic receptors. Dopamine should be avoided as first-line therapy for MI with CS based on hemodynamic and proarrhyth mogenic effects. Dobutamine is a synthetic sympathomimetic amine with posi tive inotropic action and minimal positive chronotropic activity at low doses (2.5 μg/kg per min) but moderate chronotropic activity at higher doses. Its vasodilating activity often precludes its use when a vasoconstrictor effect is required. Levosimendan may also be appealing despite a lack of randomized data but was not beneficial for organ dysfunction in sepsis and also in high-risk patients under going cardiovascular surgery. Milrinone—a phosphodiesterase-3 inhibitor and inodilator—was recently shown to have no benefit in comparison with dobutamine. MECHANICAL CIRCULATORY SUPPORT The most commonly used mechanical circulatory support (MCS) device has been the intraaortic balloon pump (IABP), which is inserted into the aorta via the femoral artery and provides passive

VSD (~4%) Mitral reg. (~7%) Free wall rupture (~2%) Heart team Surgical/intervent. closure (IC) Mitral repair/ replacement (IC) Surgery (IC) pericardiocentesis Emergency PCI of culprit lesion in case of interventional treatment (IB) Simultaneous CABG in case of surgical treatment (IB) IABP (IIA/C) Stabilization? No No No Severe neurologic deficit? Age, comorbidities? Long-term surgical MCS Bridge to recovery Bridge to transplant Destination therapy hemodynamic support. However, routine IABP use in conjunction with early revascularization (predominantly with PCI) did not reduce 30-day, 12-month, or 6-year mortality in the IABP-SHOCK II trial. IABP also had no benefit on secondary endpoints (arterial lactate, catecholamine doses, renal function, or intensive care sever ity of illness unit scores). IABP is no longer recommended for CS with LV failure. Active MCS devices to support the left, right, or both ventricles can be placed percutaneously or surgically. Temporary percutaneous MCS can be used as bridge to recovery, to surgically implanted dura ble devices, to heart transplantation, or as a temporizing measure when the neurologic status is uncertain. Percutaneous MCS, includ ing the TandemHeart and Impella devices, and also venoarterial extracorporeal membrane oxygenation (VA-ECMO) have been used in patients not responding to standard treatment (catecholamines, fluids, and IABP) and also as a first-line treatment. Active percu taneous MCS results in better hemodynamic support compared to IABP. However, the appropriate role of MCS, in particular Impella, is uncertain because a positive impact on clinical outcomes or mortality has not yet been demonstrated in trials or meta-analyses. More recent observational data with matched comparisons compris ing several ten thousands of patients even showed higher mortal ity and more complications with active devices such as Impella. Recently the results of the Danish-Germany (DanGer) shock trial

TABLE 316-2 Utility of the Echocardiogram in Cardiogenic Shock or Pulmonary Edema CLINICAL QUESTION INFORMATION Ventricular function Predominantly left, right, or biventricular involvement Etiology Acute Myocardial Infarction • Extent of infarction/myocardium in jeopardy • Status of the nonculprit infarct zone • Presence of mechanical complications Acute/Chronic Valvular Insufficiency/Obstruction/ Stenosis (Native/Prosthetic) • Etiology: endocarditis; degenerative valve disease • Location and hemodynamic consequences Dynamic Left Ventricular Tract Obstruction Takotsubo Syndrome Cardiac Tamponade Circumferential versus localized effusion Route of pericardiocentesis if indicated Acute Pulmonary Embolism Right ventricular function Pulmonary artery pressure Presence of clot in transition/patent foramen

ovale Acute Aortic Syndrome Nature and extent of dissection Degree of aortic insufficiency Presence of pericardial effusion Hemodynamics Volume assessment by inferior vena cava diameter and inspiratory collapse Estimated pulmonary artery systolic pressure Estimated left atrial pressure Therapeutic guidance Guide vasoactive support Monitor response to therapy Mechanical circulatory support decisions Catheter position and guidance Pulmonary Pleural effusion Lung edema Pneumothorax Pulmonary infiltration TABLE 316-3 Hemodynamic Patternsa RA, mmHg RVS, mmHg RVD, mmHg PAS, mmHg PAD, mmHg PCW, mmHg CI, (L/min)/m2 SVR, (dyn · s)/cm5 Normal values <6 <25 0–12 <25 0–12 <6–12 ≥2.5 (800–1600) MI without pulmonary edemab — — — — — ~13 (5–18) ~2.7 (2.2–4.3) — Pulmonary edema ↔↑ ↔↑ ↔↑ ↑ ↑ ↑ ↔↓ ↑ Cardiogenic shock LV failure ↔↑ ↔↑ ↔↑ ↔↑ ↑ ↑ ↓ ↔↑ RV failurec ↑ ↓↔↑d ↑ ↓↔↑d ↔↓↑d ↓↔↑d ↓ ↑ Cardiac tamponade ↑ ↔↑ ↑ ↔↑ ↔↑ ↔↑ ↓ ↑ Acute mitral regurgitation ↔↑ ↑ ↔↑ ↑ ↑ ↑ ↔↓ ↔↑ Ventricular septal rupture ↑ ↔↑ ↑ ↔↑ ↔↑ ↔↑ ↑PBF ↓SBF ↔↑ Hypovolemic shock ↓ ↔↓ ↔↓ ↓ ↓ ↓ ↓ ↑ Septic shock ↓ ↔↓ ↔↓ ↓ ↓ ↓ ↑ ↓ aThere is significant patient-to-patient variation. Pressure may be normalized if cardiac output is low. bForrester et al classified non-reperfused MI patients into four hemodynamic subsets. (From JS Forrester et al: N Engl J Med 295:1356, 1976.) PCW pressure and CI in clinically stable subset 1 patients are shown. Values in parentheses represent range. c"Isolated" or predominant RV failure. dPCW and pulmonary artery pressures may rise in RV failure after volume loading due to RV dilation and right-to-left shift of the interventricular septum, resulting in impaired LV filling. When biventricular failure is present, the patterns are similar to those shown for LV failure. Abbreviations: CI, cardiac index; LV, left ventricular; MI, myocardial infarction; P/SBF, pulmonary/systemic blood flow; PAS/D, pulmonary artery systolic/diastolic; PCW, pulmonary capillary wedge; RA, right atrium; RV, right ventricular; RVS/D, right ventricular systolic/diastolic; SVR, systemic vascular resistance. Source: Table prepared with the assistance of Krishnan Ramanathan, MD.

were published: in 360 selected patients with anterior ST-elevation myocardial infarction without high risk of hypoxic brain injury comparing a microaxial flow pump with 3.5 L/min versus standard of care, the active MCS was associated with better 180-day outcome. Despite the long recruitment period, the narrow inclusion criteria, and several open questions such as a high increase in mortality from 30 days to 6-months in the control arm, a very short ICU time in the control group, and the highest ever reported renal replacement therapy frequency in the active MCS arm, this randomized trial is an important study supporting the use of MCS in selected patients.

Recent randomized data of VA-ECMO versus control in CS did not show a survival benefit in the ECLS-SHOCK trial. VAECMO was accompanied by significantly higher complications, such as moderate/severe bleeding or peripheral ischemic complica tions. The lack of mortality benefit and

higher complication rates with VA-ECMO use were confirmed in an individual patient data meta-analysis. CHAPTER 316 Surgically implanted devices can support the circulation as bridging therapy for cardiac transplant candidates or as destination therapy (Chap. 271). Assist devices should be used selectively in suitable patients based on decisions by a multidisciplinary team with expertise in the selection, implantation, and management of MCS devices (Fig. 316-3). Cardiogenic Shock and Pulmonary Edema Prognosis The expected death rates for patients with MI com plicated by CS range widely based on age, severity of hemodynamic abnormalities, severity of clinical hypoperfusion (arterial lactate, renal function), and performance of early revascularization. The recently introduced IABP-SHOCK II score predicts prognosis based on six read ily available variables: age >73 years; prior stroke; glucose at admission

> 10.6 mmol/L (191 mg/dL); creatinine at admission >132.6 µmol/L (1.5 mg/dL); Thrombolysis in Myocardial Infarction (TIMI) flow grade after PCI <3; and arterial blood lactate at admission >5 mmol/L. It also may help guide treatment strategies. The SCAI CS severity definition with stages A to E is also helpful in prognosis estimation. ■ ■SHOCK SECONDARY TO RIGHT

VENTRICULAR INFARCTION Persistent CS due to predominant RV failure accounts for only 5% of CS complicating MI. It often results from proximal right coronary artery occlusion. The salient features are relatively high right atrial pressures, RV dilation and dysfunction, and only mildly or moderately depressed LV function. High right-sided pressures may be absent

without volume loading. However, CS often has overlap combinations of both RV and LV ischemia, given a shared septum and the effect of ventricular interdependence on RV function. Management of isolated RV CS includes fluid administration to optimize right atrial pressure (10–15 mmHg); avoidance of excess fluids, which shifts the interven tricular septum into the LV; catecholamines; early reestablishment of infarct-artery flow; and possibly right-sided MCS.

■ ■MITRAL REGURGITATION (See also Chap. 286) Acute severe MR due to papillary muscle dys function and/or rupture may complicate MI and result in CS and/or pulmonary edema. This complication most often occurs on the first day, with a second peak several days later. The diagnosis is confirmed by echocardiography (Table 316-2). Afterload reduction with IABP and, if tolerated, vasodilators to reduce pulmonary edema is recom mended as a bridge to surgery or interventional treatment. Mitral valve repair or reconstruction is the definitive therapy and should be performed early in the course in suitable candidates. Other options include percutaneous edge-to-edge repair, which has been successful in case series and registries (Fig. 316-3). PART 8 Critical Care Medicine ■ ■VENTRICULAR SEPTAL RUPTURE (See also Chap. 286) VSR complicating MI is a relatively rare event associated with very high mortality if CS is present (>80%). The incidence of infarct-related VSR without reperfusion was 1–2% but has decreased to 0.2% in the era of reperfusion. VSR occurs a median of 24 h after infarction but may occur up to 2 weeks later. Echocar diography demonstrates shunting of blood from the left to the right ventricle and may visualize the opening in the interventricular septum. Current American guidelines recommend immediate surgical VSR closure, irrespective of the patient’s hemodynamic status, to avoid further hemodynamic deterioration. European guidelines differ with a more selective approach based on

heart team evaluation. IABP sup port as a bridge to surgery is recommended based on expert opinion. Active MCS may, however, be more appropriate for stabilization of the patient. Given high mortality, suboptimal surgical results, and the ineli gibility for surgery of many patients, interventional percutaneous VSR umbrella device closure has been developed. Results of interventional VSR closure suggest a similar outcome as surgery. The heart team should decide how to close the VSR (Fig. 316-3). ■ ■FREE WALL RUPTURE Myocardial rupture is a dramatic complication of MI that is most likely to occur during the first week after the onset of symptoms. The clinical presentation typically is a sudden loss of pulse, BP, and consciousness with ongoing sinus rhythm on ECG (pulseless electri cal activity) due to cardiac tamponade (Chap. 281). Free wall rupture may also result in CS due to subacute tamponade when the pericar dium temporarily seals the rupture sites. Definitive surgical repair is required (Fig. 316-3). ■ ■ACUTE FULMINANT MYOCARDITIS (See also Chaps. 266–270) Myocarditis can mimic acute MI with ST abnormalities or bundle branch block on the ECG and marked elevation of cardiac markers. Acute myocarditis causes CS in a small proportion of cases. These patients are typically younger than those with CS due to acute MI and often do not have typical ischemic chest pain. Echocar diography usually shows global LV dysfunction. Initial management is the same as for CS complicating acute MI but does not involve revas cularization. Endomyocardial biopsy is recommended to determine the diagnosis and need for immunosuppressives for entities such as giant cell myocarditis. Refractory CS can be managed with MCS. ■ ■PULMONARY EDEMA The etiologies and pathophysiology of pulmonary edema are discussed in Chap. 39. Diagnosis Acute pulmonary edema usually presents with the rapid onset of dyspnea at rest, tachypnea, tachycardia, and severe hypoxemia. Crackles and wheezing due to alveolar flooding, increased airway fluid,

and airway compression from peribronchial cuffing may be audible. Release of endogenous catecholamines often causes hypertension. It is often difficult to distinguish between cardiogenic and noncardio genic causes of acute pulmonary edema. Echocardiography may identify systolic and diastolic ventricular dysfunction and valvular lesions. ECG ST elevation and evolving Q waves are usually diagnostic of acute MI and should prompt immediate institution of MI protocols and coronary artery revascularization therapy (Chap. 286). Brain natriuretic peptide levels, when substantially elevated, support heart failure as the etiology of acute dyspnea with pulmonary edema (Chap. 264). The use of a PAC permits measurement of pulmonary capillary wedge pressures (PCWP) and helps differentiate high-pressure (car diogenic) from normal-pressure (noncardiogenic) causes of pulmo nary edema. Pulmonary artery catheterization is indicated when the etiology of the pulmonary edema is uncertain, when edema is refrac tory to therapy, or when it is accompanied by refractory hypotension. Data derived from use of a PAC often alter the treatment plan, but no impact on mortality rates has been demonstrated. TREATMENT Pulmonary Edema The treatment of pulmonary edema depends on the specific etiol ogy. As an acute, life-threatening condition, a number of mea sures must be applied immediately to support the circulation, gas exchange, and lung mechanics. Simultaneously, conditions that fre quently complicate pulmonary edema, such as infection, acidemia, anemia, and acute kidney dysfunction, must be corrected. SUPPORT OF OXYGENATION AND VENTILATION Patients with acute cardiogenic pulmonary edema generally have an identifiable cause of acute LV failure—such as arrhythmia, ischemia/ infarction, or myocardial decompensation (Chap. 264)—that may be rapidly treated, with improvement in gas exchange. In contrast, noncardiogenic edema usually resolves much less quickly, and most patients require mechanical ventilation. Oxygen Therapy Support of oxygenation is essential to ensure adequate O_2 delivery to peripheral tissues, including the heart. Generally,

the goal is O2 saturation of 92% or more, but very high saturation (>98%) may be detrimental. For non-CS acute hypoxemic respiratory failure patients with normal Paco2, O2 administration by high-flow nasal cannula for acute hypoxemic respiratory failure has better outcomes than use of bilevel positive airway pressure (BiPAP). Positive-Pressure Ventilation Pulmonary edema increases the work of breathing and the O2 requirements of this work, imposing a significant physiologic stress on the heart. When oxygenation or ventilation is not adequate despite supplemental O2, positive-pressure ventilation by face or nasal mask or by endotracheal intubation should be initiated. Noninvasive ventilation (NIV) (Chap. 313) can rest the respiratory muscles, improve oxygenation and cardiac function, and reduce the need for intubation. While NIV is believed effective for cardiogenic pulmonary edema, Cochrane analyses have not yet substantiated this benefit. In refractory cases, mechanical ventilation can relieve the work of breathing more completely than can NIV. Helmet ventilation is a new technique for ventilation with positive pressure without intubation. Mechanical ventilation with positive end-expiratory pressure can have multiple beneficial effects on pulmonary edema, as it: (1) decreases both preload and afterload, thereby improving cardiac function; (2) redistributes lung water from the intraalveolar to the extraalveolar space, where the fluid interferes less with gas exchange; and (3) increases lung volume to avoid atelectasis. Renal Replacement Therapy For pulmonary edema patients with refractory volume overload, metabolic acidosis (pH <7.15–7.25), hypoxemia, and/or persistent hyperkalemia, renal replacement therapy should be considered. For patients who are hypotensive or require ionotropic support, continuous renal replacement therapy usually is better tolerated than intermittent hemodialysis.

REDUCTION OF PRELOAD In most forms of pulmonary edema, the quantity of extravascular lung water is determined by a combination of the PCWP, the pul monary vascular permeability, and the intravascular volume status. Diuretics The loop diuretics furosemide, bumetanide, and torse mide are effective in most forms of pulmonary edema, even in the presence of hypoalbuminemia, hyponatremia, or hypochloremia. Furosemide is also a venodilator that rapidly reduces preload before any diuresis occurs and is the diuretic of choice. The initial dose of furosemide should be ≤0.5 mg/kg, but a higher dose (1 mg/kg) is required in patients with renal insufficiency, chronic diuretic use, or hypervolemia or after failure of a lower dose. Combinations of diuretics and/or continuous infusion are helpful to achieve the desired degree of diuresis in selected patients. Nitrates Nitroglycerin and isosorbide dinitrate act predominantly as venodilators but have coronary vasodilating properties as well. Their onset is rapid, and they are effectively administered by a variety of routes. Sublingual nitroglycerin (0.4 mg × 3 every 5 min) is first-line therapy for acute cardiogenic pulmonary edema. If pul monary edema persists in the absence of hypotension, sublingual may be followed by IV nitroglycerin, commencing at 5–10 μg/min. IV nitroprusside (0.1–5 μg/kg per min) is a potent venous and arte rial vasodilator. It is useful for patients with pulmonary edema and hypertension but is not recommended in states of reduced coronary artery perfusion. It requires close monitoring and titration using an arterial catheter for continuous BP measurement. Morphine Given in 2- to 4-mg IV boluses, morphine is a transient venodilator that reduces preload while relieving dyspnea and anxi ety. These effects can diminish stress, catecholamine levels, tachy cardia, and ventricular afterload in patients with pulmonary edema and systemic hypertension. However, some registry trials showed increased mortality with use of morphine. Angiotensin-Converting Enzyme (ACE) Inhibitors ACE inhibi tors reduce both afterload and preload and are recommended for hypertensive patients. A low dose of a short-acting agent may be initiated and followed by increasing oral doses. In acute MI with heart failure, ACE inhibitors reduce

short- and long-term mortality rates. The optimal starting point of ACE inhibitors has not been tested so far. Other Preload-Reducing Agents IV recombinant brain natriuretic peptide (nesiritide) is a potent arterial and venous vasodilator with diuretic properties and is effective in the treatment of cardiogenic pulmonary edema. It should be reserved for refractory patients and is not recommended in the setting of ischemia or MI. Endothelin antagonists are being studied as they inhibit vasoconstriction and can improve cardiac output and decrease PCWP. Physical Methods In nonhypotensive patients, venous return can be reduced by use of the sitting position with the legs dangling along the side of the bed. Inotropic and Inodilator Drugs The sympathomimetic amines dopamine and dobutamine (see above) are potent inotropic agents. The bipyridine phosphodiesterase-3 inhibitors (inodilators), such as milrinone (50 μg/kg followed by 0.25–0.75 μg/kg per min), stimulate myocardial contractility while promoting peripheral and pulmonary vasodilation. Inodilators may be helpful in selected patients with cardiogenic pulmonary edema and severe LV dys function, but there is little published clinical data. Angiotensin II is a vasoconstrictor and possible positive inotrope that can raise BP in many types of shock. It is expensive and has not been shown to have additive or superior benefit to other vasopressors in CS. Digitalis Glycosides Once a mainstay of treatment because of their positive inotropic action (Chap. 264), digitalis glycosides are rarely used at present. However, they may be useful for control of ventricular rate in patients with rapid ventricular response to atrial fibrillation or flutter and LV dysfunction with pulmonary edema,

because they do not have the negative inotropic effects of other drugs that inhibit atrioventricular nodal conduction.

Intraaortic Balloon Counterpulsation IABP (Chap. 271) may be helpful in rare instances of acute MR but is not typically used for pulmonary edema with CS. Treatment of Tachyarrhythmias and Atrioventricular Resynchroniza tion (See also Chap. 259) Sinus tachycardia or atrial fibrillation can result from elevated left atrial pressure and sympathetic stimulation. Tachycardia itself can limit LV filling time and raise left atrial pres sure further. Although relief of pulmonary congestion will slow the sinus rate or ventricular response in atrial fibrillation, a primary tachyarrhythmia may require cardioversion. In patients with reduced LV function and without atrial contraction or with lack of synchro nized atrioventricular contraction, placement of an atrioventricular sequential pacemaker should be considered (Chap. 251). CHAPTER 316 Reduction in Pulmonary Vascular Permeability At present, no clinical therapies have been demonstrated as clinically effective to reduce the “leakiness” of the pulmonary capillaries. Stimulation of Alveolar Fluid Clearance A variety of drugs and cellular therapies can stimulate alveolar epithelial ion transport and upregulate the clearance of alveolar solute and water, but this strat egy has not been proven beneficial in clinical trials thus far. Cardiogenic Shock and Pulmonary Edema SPECIAL CONSIDERATIONS Risk of Iatrogenic Cardiogenic Shock In the treatment of pul monary edema, vasodilators lower BP, and their use, particularly in combination, may lead to hypotension, coronary artery hypoperfu sion, and shock (Fig. 316-1). In general, patients with a hypertensive response to pulmonary edema tolerate and benefit from these med ications. In normotensive patients, low doses of single agents should be instituted sequentially, as needed, and with close monitoring. Acute Coronary Syndromes (See also Chap. 286) Acute STEMI complicated by pulmonary edema is associated with in-hospital mortality rates of 20–40%. After immediate stabilization, coronary artery blood flow must be reestablished rapidly. Early primary PCI is the method of choice; alternatively, a fibrinolytic agent should be administered. Early coronary angiography and revascularization by PCI or CABG also are indicated for patients with non–ST-segment elevation acute coronary syndrome. Takotsubo Syndrome

Takotsubo syndrome is an acute revers ible heart failure syndrome characterized by acute onset of leftsided heart failure with reversible ST-segment elevation and some increase in troponin levels, usually triggered by a major physical or emotional, stressful event. At end systole, there often is the appear ance of LV apical “ballooning.” Most patients recover and return to normal ventricular function. However, prognosis is similar or even worse in comparison to patients with acute MI. Extracorporeal Membrane Oxygenation (ECMO) For patients with acute, severe, noncardiogenic edema with a potential rapidly reversible cause, ECMO may be considered in highly selected patients as a temporizing supportive measure to achieve adequate gas exchange, with current survival to discharge rates of 50–60%. Usually, venovenous ECMO is used in this setting. ECMO can func tion as a bridge to transplantation or other interventions. Unusual Types of Edema Specific etiologies of pulmonary edema may require particular therapy. Reexpansion pulmonary edema can develop after removal of longstanding pleural space air or fluid. These patients may develop hypotension or oliguria with pulmonary edema resulting from rapid fluid shifts into the lung. Diuretics and preload reduction are contraindicated, and intravascular volume repletion often is needed while supporting oxygenation and gas exchange. High-altitude pulmonary edema often can be prevented by use of dexamethasone, calcium channel–blocking drugs, or long-acting inhaled β2-adrenergic agonists. Treatment includes descent from altitude, bed rest, oxygen, and, if feasible, inhaled NO; nifedipine may also be effective.

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