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ICU Treatment of Severe Acute Pancreatitis

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Introduction

Acute pancreatitis remains a complex, progressive, and variable acute inflammatory syndrome of the pancreas. In some cases, the inflammatory response is so severe that a sequence of systemic inflammation defined by the systemic inflammatory response syndrome (SIRS), capillary leak syndrome (CLS), multiorgan dysfunction, shock, and death may occur. Patients with life-threatening complications should be managed in the intensive care unit (ICU), where early intervention and support may result in better outcomes. This chapter will focus on management following a general clinical pathway to emphasize the sequence of common events and evidence behind clinical decisions.

Pre-ICU Management

Optimal treatment begins in the clinic or emergency department (Fig. 25.1). The primary goals in early evaluation include confirming the diagnosis, detecting early signs of organ dysfunction, and initiating fluid resuscitation. Fluid resuscitation (see Chapter 26) may be the most important early intervention for stabilizing and treating patients with evolving severe acute pancreatitis.

The initial physical examination is central to assessment and proper triage. The clinical histories are variable, but sudden onset of severe, sharp, unrelenting pain with nausea and vomiting is common. In addition to a routine physical examination the clinician should focus on early signs of severe acute pancreatitis, including severe pain, anxiety, confusion, scleral icterus, diaphoresis, dry mouth, tachycardia, thready pulses, acrocyanosis, tachypnea, lung rales, and abdominal tenderness with or without rebound pain. Postural changes (e.g., supine to standing) resulting in dizziness or tachycardia suggest significant intravascular hypovolemia.

The initial laboratory assessment should include standard diagnostic tests in addition to standard laboratory tests (Box 25.1). These tests serve both as baseline values for future comparisons and early biomarkers of organ dysfunction that may require ICU management. A chest X-ray may provide early evidence of pulmonary edema and/or plural effusions [1].

Early morbidity and mortality are heralded by SIRS, as it often leads to endothelial stress [2], CLS [3] and organ dysfunction involving the lungs, cardiovascular system, intestines, and kidneys, and damage to the pancreas [4–7]. Early management focuses on fluid resuscitation and oxygenation. Patient comfort centers on treatment of pain and nausea.

Life-threatening hypovolemia in acute pancreatitis develops because of CLS, which occurs in an unpredictable subset of patients. The mechanism of hypovolemia in acute pancreatitis appears to overlap with trauma and involve epithelial cell damage, CLS, and loss of large and small proteins from the circulation into interstitial and third spaces [2,3,8]. Blood pressure may not become significantly decreased until the patient has lost 30–40% of circulating blood volume [9]. Therefore, blood pressure correlates poorly with both blood volume and cardiac output. Furthermore, the severity of the hypovolemia may be masked by splanchnic vasoconstriction and shunting of blood from the viscera to maintain circulation to the brain and peripheral organs. Hypovolemia may also be overlooked by focusing on criteria designed for sepsis or multiple trauma such as systolic blood pressure <90 mmHg [7,10].

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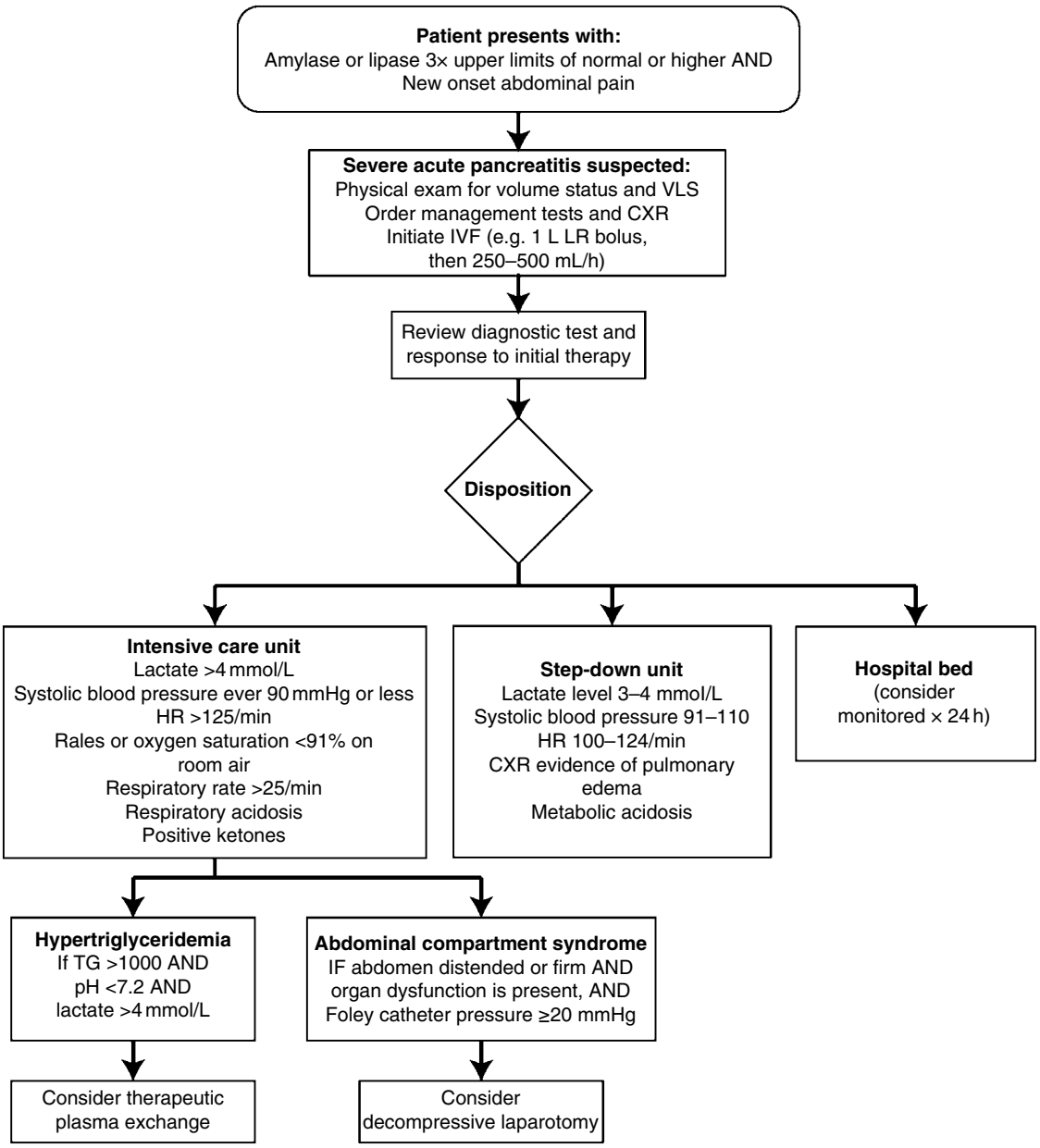

Figure 25.1 An illustrative clinical pathway for managing patients during the initial evaluation and possible admission into the intensive care unit. See text. CXR: chest x-ray; HR: heart rate; LR: lactated Ringer's solution; TG: triglyceride level; CLS: capillary leak syndrome.

Hypoperfusion and/or ischemia of visceral organs create two additional challenges to the problem of generalized tissue ischemia. First, hypoperfusion may continue long after systemic volume resuscitation has occurred, resulting in continued ischemic stress on intestinal mucosal epithelial cells, the most vulnerable cells of the gut. Second, mucosal epithelial cell injury results in breakdown of the mucosal barrier and translocation of bacteria and toxic factors that enter the circulation via the mesenteric lymphatics and drive SIRS [11,12]. Thus, in some patients, a vicious cycle develops with systemic inflammation leading to CLS, which causes intravascular hypovolemia and splanchnic vascular bed ischemia, leading to translocation of proinflammatory toxins from the gut lumen into the lymphatics that further drives systemic inflammation. Interruption of this cycle should begin with minimizing or preventing intravascular hypovolemia.

The usual systolic blood pressure of adults varies widely, so the relative change in both blood pressure and heart rate may be more important than an absolute value. A systolic blood pressure <90 mmHg, however, is likely

Box 25.1 Baseline blood-based laboratory tests

Diagnostic tests [on admission]

- Amylase level
- Lipase level
- Triglyceride level
- Calcium level

Management tests [on admission and every 6–24 hours as needed]

- Electrolytes (sodium, potassium, chloride, bicarbonate)
- Blood urea nitrogen (including pre-acute pancreatitis levels)
- Creatinine (including pre-acute pancreatitis levels)
- Blood glucose
- Complete blood count (for white blood cell count and hematocrit)
- Liver injury tests (for bile duct obstruction and aetiology)
- Albumin (including pre-acute pancreatitis levels)
- Total Protein (including pre-acute pancreatitis levels)
- Serum lactate
- Serum LDH (optional)
- Arterial blood gas (optional)

to be a *late* sign of severe intravascular hypovolemia [13]. An elevated hematocrit indicates hemoconcentration and implies significant extravasation of serum and protein-rich plasma from the bloodstream and is a harbinger of impending organ failure [3]. Elevated lactate levels also suggest that tissues may already be in shock [14]. We believe that optimal treatment includes the prevention of hypotension and shock, and resuscitation should not be delayed until signs of hemoconcentration, and shock develop.

Treatment and prevention of progressive intravascular hypovolemia must begin before the patient is transferred to the ICU. Although acute pancreatitis has been compared with septic shock and similar resuscitation algorithms suggested, the current evidence supporting goal-directed therapy, using parameters to guide either rate or total volume of resuscitation, to reduce morbidity or mortality is limited [10]. We recommend that resuscitation with balanced salt solution should be given rapidly, as soon as the diagnosis of acute pancreatitis is made, with modifications for patients with existing comorbidities [4,10]. Further research on the resuscitative strategies may help guide our approach [15].

Early use of supplemental oxygen is warranted with continuous monitoring of oxygen saturation via pulse oximetry or intermittent arterial blood gas analysis. The pulmonary edema seen in patients with severe acute pancreatitis and CLS is usually due to endothelial cell injury and extravasation of plasma, not fluid overload. Therefore, the treatment should be positive pressure ventilation and not diuresis, unless the patient is absolutely volume overloaded.

For pain we recommend hydromorphone 0.5–2.0 mg intravenously every 15 minutes while the respiratory rate is >10 and systolic blood pressure is >90 mmHg. However, no differences between opiates were demonstrated in systematic reviews of variable quality clinical studies [16,17]. Opiates primarily used in the United States and new studies are needed to determine necessity and utility. For nausea we give ondansetron 4–8 mg intravenously every 6 hours as needed.

Special Considerations

As in trauma, management decisions made in the early minutes and hours of care have significant downstream consequences. The emergency in severe acute pancreatitis is fluid management and tissue oxygenation within the context of systemic inflammation. But unlike trauma where the insult is rapid and finite, the systemic inflammation of acute pancreatitis evolves, so continued attention to the evolution of the process over the first 24 hours is critical.

We strongly discourage the use of contrast computed tomography (CT) scan in early severe acute pancreatitis. The diagnosis can almost always be made by the combination of typical pain and elevated serum levels of pancreatic digestive enzymes [5,7]. Although contrast-enhanced CT scan remains useful for detecting and quantifying pancreatic necrosis and/or fluid collections, there are no urgent interventions, and the evaluation can be delayed for days. Early contrast CT poses at least two risks. First, the contrast may worsen the severity of pancreatic necrosis, as well as kidney injury in patients, especially if there is poor perfusion from hypovolemia and/or shunting of blood from visceral organs. Second, the process of obtaining a CT may interrupt evaluation and treatment, or delay transfer to the ICU. However, CT or other abdominal imaging modalities may be required if the diagnosis is in question.

Gallstone pancreatitis occurs when small gallstones become lodged at the sphincter of Oddi and trigger intrapancreatic digestive enzyme activation and acute pancreatitis. In some cases, the gallstone remains lodged, whereas in others the stone passes on its own. Although there used to be great enthusiasm for urgent endoscopic retrograde cholangiopancreatography, biliary sphincterotomy, and stone removal, randomized studies failed to demonstrate a benefit for early intervention [18]. The

exceptions are cases where an impacted gallstone results in ascending bacterial cholangitis [18]. This condition represents an urgent complication that requires a therapeutic intervention. In this setting, antibiotics should be started immediately. However, the priority of an ERCP is secondary to fluid resuscitation, airway management, and patient stabilization.

Indications for ICU Admission

Early and appropriate treatment of patients with acute pancreatitis may result in rapid resolution of signs and symptoms of more severe disease. In these cases, it is reasonable for patients to be treated and monitored on a step-down unit until the clinical course of the patient dictates a change in care level.

The severe early consequences of acute pancreatitis are related to organ dysfunction and damage rather than SIRS itself. The recommendations of the Revised Atlanta Criteria recommends that patients with SIRS be considered as high risk for organ failure, but that severity is based on organ failure that persists for at least 48 hours to classify patients as truly severe [7]. The Revised Atlanta Criteria defines organ failure based on the Modified Marshall Score of 2 or more in the respiratory system (PaO2/FiO2 of ≥300), renal system (serum creatinine of ≥170 μmol/L or ≥1.9 mg/dL) or cardiovascular system (systolic blood pressure of <90 and not fluid responsive) [7]. However, we are concerned that the criteria are too severe and too late for early triage, increasing risk of avoidable organ damage and unexpected cardiopulmonary arrest of patients admitted to unmonitored regular hospital floors or at home.

The problem with the Modified Marshall Score criteria is that they do not account for the baseline state of the patient and reflect the eventual development of severe organ dysfunction and failure to meet criteria. In the early hours of acute pancreatitis evaluation, it is most important to determine which patient is evolving into organ failure and initiate mitigation strategies such as early fluid resuscitation which may prevent hypotension despite severe underlying pathophysiology. We recommend early identification of patients with evolving organ failure using the Komara criteria [3], which considers pre-acute pancreatitis biomarker status and more accurately distinguishes patients with more severe disease. Specifically, early organ failure (e.g., within the first 72 hours) is likely if the patient has a rise of haematocrit from baseline of >3 (odds ratio 17.7, $P = 0.014$), if both BUN and creatinine levels are increasing from pre-acute pancreatitis levels (and continue rising), and if serum albumin and total protein are dropping. The drop in albumin, and especially total protein appear to reflect endothelial cell stress or injury with CLS, which takes 24 hours to develop [3]. Multiple studies now demonstrate that dropping and low serum albumin are associated with multiorgan failure and severe outcomes [3,19–21]. Multiple prognostic scores may also be useful for predicting later organ failure [22].

We recommend ICU admission for patients with evolving or persistent organ dysfunction who require a high level of care with frequent adjustments to the care plan. Examples include patients with lactate >4 mmol/L, systolic blood pressure at any time <90 mmHg, need for vasopressors, an ongoing heart rate of >125 per minute, rales on lung exam or oxygen saturation <91% on room air, a respiratory rate >25 per minute, any respiratory acidosis or positive serum ketones. In addition, patients with SIRS and CLS (based on Komara Criteria above) may require ICU admission for invasive monitoring of intravascular volume, and impending cardiac and/or pulmonary dysfunction.

ICU Treatment of Severe Acute Pancreatitis

The evolution of severe acute pancreatitis dictates the concerns and management strategies over the first days of disease. The initial phase (0–48 hours after onset of pain) reflects the magnitude of the acute inflammatory response with SIRS, CLS, and early organ dysfunction of the cardiovascular system, lungs, and kidneys. The second phase (48–120 hours after onset of pain) focuses on managing recovery of organ systems from injury and preventing secondary problems such as infection in immunocompromised patients from the compensatory anti-inflammatory response syndrome (CARS) (23).

Early ICU Management (0–48 Hours from Onset of Pain)

Managing patients with acute pancreatitis who require ICU admission is best done by a multidisciplinary team including intensivists and specialists in the medical and surgical management of pancreatitis.

Management of Cardiovascular Dysfunction

Hypotension may be the result of inadequate cardiac output from intravascular volume depletion, reduced systemic vascular resistance, or both. Early therapy

should center on restoration of adequate circulating blood volume to ensure adequate oxygen delivery while simultaneously avoiding exuberant fluid administration, which leads to volume overload and potentially worse outcomes [24]. Ongoing hypotension despite volume resuscitation will require vasopressor support. We guide our volume resuscitation and the initiation of pressors based on repeated physical exam, biochemical markers of perfusion (lactate and mixed venous oxygen saturations), and dynamic measures of preload responsiveness, such as pulse pressure variation on the arterial line of intubated patients [25–27].

If the patient remains hypotensive after preload is optimized, we initiate pressors for maintenance of perfusion pressure. We target a mean arterial pressure of ≥65 mmHg. Once again, there are few study results to guide us in our choice of pressor. The literature suggests that neither norepinephrine nor epinephrine have a mortality benefit for patients with septic shock [14,28]. However, epinephrine may increase lactate levels despite achieving adequate perfusion pressure, so we start with norepinephrine. We do not routinely add vasopressin unless the patient exhibits significant complications from high-dose catecholamine therapy such as tachyarrhythmias [29]. Careful documentation of both fluid input and output is useful for gauging overall fluid balance and the magnitude of CLS.

Management of Pulmonary Dysfunction

Acute respiratory distress syndrome (ARDS) is a well-recognized complication of acute pancreatitis. Initial management with supplemental oxygen may prove inadequate and many patients with ARDS will require more aggressive care. High-flow oxygen through a nasal cannula provides heated and humidified oxygen at flow rates high enough to develop some continuous positive airway pressure. In addition, high-flow oxygen may be more comfortable than noninvasive ventilation [30].

All patients who require intubation and mechanical ventilation for ARDS should be initially managed with a tidal volume of 6 mL/kg predicted body weight. Respiratory rates are adjusted to achieve a pH between 7.30 and 7.45 if possible. Positive end-expiratory pressure (PEEP) and fraction of inspired oxygen (FiO_2) should be titrated to maintain an arterial PaO_2 of between 55 and 80 mmHg (31). Titrating PEEP or FiO_2 to achieve a $PaO_2 > 80$ mmHg may improve arterial blood gas values but has not been shown to improve survival [32]. If hypoxia persists (i.e., a PaO_2/FiO_2 ratio of <150 mmHg) and PEEP and FiO_2 levels exceed 10 and 0.6, respectively, we consider neuromuscular blockade [33] and initiate prone position ventilation [34] early.

Management of Abdominal Compartment Syndrome

Abdominal compartment syndrome is a pathophysiologic process arising from increased tissue fluid within the peritoneal and/or retroperitoneal space. Like other compartment syndromes, when the abdominal cavity can no longer expand, further fluid collection results in increases in abdominal pressure with subsequent decreases in perfusion and ischemia to intra-abdominal organs. In patients with acute pancreatitis, swelling from pancreatic necrosis, ileus with gas distension, fluid collections, and volume overload from resuscitation may lead to abdominal compartment syndrome. Abdominal compartment syndrome is suspected on physical examination when the abdomen is firm and/or distended.

Intra-abdominal pressure is the steady-state pressure within the abdominal cavity and is measured by instilling 25 mL of sterile saline through the Foley catheter and measuring the resultant pressure at end expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the midaxillary line [35]. A normal intra-abdominal pressure in critically ill adults is 5–7 mmHg. Intra-abdominal hypertension is a sustained pressure ≥12 mmHg.

Abdominal compartment syndrome is a sustained intra-abdominal pressure of ≥20 mmHg with new organ dysfunction or failure. Although some patients may respond to a trial of sedation and neuromuscular blockade (relaxing the abdominal wall and thereby decreasing intra-abdominal pressure) and nasogastric tube decompression, many patients with acute pancreatitis and abdominal compartment syndrome will need a decompressive laparotomy.

Management of Metabolic Derangements

Hypertriglyceridemia

Hypertriglyceridemic acute pancreatitis represents a spectrum of underlying genetic disorders and metabolic risks such as diabetes mellitus and obesity. Triglycerides alone are inert. However, it is believed that in the presence of lipase(s), the triglycerides are hydrolyzed to free fatty acids (FFA), and it is the FFA that are toxic, especially unsaturated FFA [36–38]. Hypertriglyceridemia is associated with more severe acute pancreatitis and persistent organ failure [39] and may require special attention. Thus, while the focus of physicians treating hypertriglyceridemic acute pancreatitis in the past has often been on reducing the triglyceride levels, the focus should be on clearing FFA [39]. Serum concentrations of

FFA are a function of production and clearance. The lipolysis of triglycerides normally occurs within tissues such as muscle, fat, and visceral organs by lipoprotein lipase (LPL), a regulated enzyme. FFA are cleared by these tissues, with excess FFA binding to albumin and transported to the liver where FFA are transferred from albumin to the hepatocytes. In acute pancreatitis, the controlled hydrolysis of triglycerides by LPL is disrupted with the addition of pancreatic lipase(s) that also catalyzes triglycerides to FFA in an unregulated way, overwhelming the capacity of the body to manage the FFA pool generated by LPL, and leading to lipotoxicity. In this case, management of the FFA-associated toxicity should focus on prevention of hydrolysis of triglycerides by LPL (e.g., fluid resuscitation and maintaining good hydration, avoiding heparin) by (theoretically) inhibiting pancreatic lipases [36], and by facilitating clearance of FFA from the serum with insulin infusion or apheresis/plasma exchange [40]. In addition to driving SIRS, FFA can block mitochondrial function, leading to lactic acidosis (pH <7.2, lactate >4 mmol/L), often seen with low calcium (e.g., calcium <8.3 mg/dL) [41]. This requires emergency intervention in the ICU, especially in the presence of liver and/or kidney dysfunction. Note that a similar syndrome of lactic acidosis occurs with complications of metformin use.

Diabetic Ketoacidosis with Acute Pancreatitis

Acute pancreatitis often develops in patients with diabetic ketoacidosis (DKA). The mechanism triggering acute pancreatitis appears to be linked to low pH. In a study of 100 subjects with DKA the subjects with coexisting acute pancreatitis had more severe metabolic acidosis (mean pH 7.15 vs. 7.31; $P = 0.0001$) and higher anion gap (38.17 mEq/L vs. 25.16 mEq/L; $P = 0.0001$) [42,43]. These patients may also have hypertriglyceridemia [44]. In these cases, addressing insulin deficiency, acidosis, and hydration results in rapid improvement.

Nutrition Support

Early nutrition support is associated with improved outcomes in patients with acute pancreatitis, and enteral feeding is superior to total parenteral nutrition (TPN) when feasible [45,46]. However, ICU patients are typically complex with confounding medial conditions, each case is unique, and multidisciplinary management may be required. Nutrition support is covered in Chapter 26.

Late ICU Management (>48 Hours after the Onset of Pain)

Visceral organs share a compartment and regulation of blood flow. Thus, damage to one organ should raise awareness of damage to others. The easiest organ to monitor is the kidney by following serum creatinine levels and blood urea nitrogen (BUN). The increase of serum creatinine and BUN levels over the first 24–72 hours usually indicates pre-renal azotemia [3] and remains among the best predictors of pancreatic necrosis and persistent organ failure [47,48]. Acute kidney injury in acute pancreatitis represents one component of a common mechanism of injury for multiple visceral organs (i.e., kidneys, pancreas, and intestine) that are damaged by hypoperfusion and ischemia [3]. Intestinal ileus may be a parallel sign of visceral organ ischemia. Early recognition of high risk for pancreatic necrosis determines future management strategies, and thus further evaluation is warranted.

After resuscitation and stabilization, abdominal imaging remains central to the eventual evaluation of pancreatic morphology, intra-abdominal fluid collections, and other complications. The radiologic evaluation and staging of severe acute pancreatitis are covered in Chapter 25.

Alcohol Withdrawal Syndrome

Alcohol abuse is a common cause of severe acute pancreatitis and alcohol withdrawal may be a complication encountered in the late ICU phase. We start treatment with escalating doses of benzodiazepines [49]. Maximal doses of benzodiazepines are defined by their diluent, propylene glycol, which can have potentially toxic effects. For benzodiazepine-resistant alcohol withdrawal syndrome, we add either phenobarbital or ketamine.

Management of Infectious Risks

The use of antibiotics is discussed in Chapter 28. The management of infected pancreatic necrosis is discussed in Chapters 29–31.

Transition Planning

As the clinical course of the patient becomes clear and the intensity of organ support is reduced, transition out of the ICU must be considered. We consider transfer out of the ICU when the organ system dysfunction that necessitated ICU admission has resolved.

References

1 Platz E, Jhund PS, Campbell RT, McMurray JJ. Assessment and prevalence of pulmonary oedema in contemporary acute heart failure trials: a systematic review. Eur J Heart Fail 2015;17(9):906–916.
2 Whitcomb DC, Muddana V, Langmead CJ et al. Angiopoietin-2, a regulator of vascular permeability in inflammation, is associated with persistent organ failure in patients with acute pancreatitis from the United States and Germany. Am J Gastroenterol 2010;105(10):2287–2292.
3 Komara NL, Paragomi P, Greer PJ et al. Severe acute pancreatitis: capillary permeability model linking systemic inflammation to multiorgan failure. Am J Physiol Gastrointest Liver Physiol 2020;319(5):G573–G583.
4 Whitcomb DC. Acute pancreatitis. N Engl J Med 2006;354(20):2142–2150.
5 Working Group IAPAPAAPG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13(4 Suppl 2):e1–15.
6 Dellinger EP, Forsmark CE, Layer P et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. Ann Surg 2012;256(6):875–880.
7 Banks PA, Bollen TL, Dervenis C et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62(1):102–111.
8 Ganter MT, Cohen MJ, Brohi K et al. Angiopoietin-2, marker and mediator of endothelial activation with prognostic significance early after trauma? Ann Surg 2008;247(2):320–326.
9 Taylor BS, Harbrecht BG. The physiologic response to injury. In: Peitzman AB, Rhodes MD, Schwab CW, Yearly DM, Favian TC, eds. The Trauma Manual. 2nd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2002: 21–22.
10 Vege SS, DiMagno MJ, Forsmark CE, Martel M, Barkun AN. Initial medical treatment of acute pancreatitis: American Gastroenterological Association Institute technical review. Gastroenterology 2018;154(4):1103–1139.
11 Mittal A, Middleditch M, Ruggiero K et al. Changes in the mesenteric lymph proteome induced by hemorrhagic shock. Shock 2010;34(2):140–149.
12 Adams CA, Jr, Hauser CJ, Adams JM et al. Trauma-hemorrhage-induced neutrophil priming is prevented by mesenteric lymph duct ligation. Shock 2002;18(6):513–517.
13 Eastridge BJ, Salinas J, McManus JG et al. Hypotension begins at 110 mmHg: redefining "hypotension" with data. J Trauma 2007;63(2):291–297; discussion 297–9.
14 Dellinger RP, Levy MM, Carlet JM et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36(1):296–327.
15 Bolado F, Buxbaum JL, Vaillo-Rocamora A, Cardenas-Jaen K, Maisonneuve P, de-Madaria E. Early weight-based aggressive vs. non-aggressive goal-directed fluid resuscitation in the early phase of acute pancreatitis: an open-label multicenter randomized controlled trial (the WATERFALL trial), design, and rationale. Front Med (Lausanne) 2020;7:440.
16 Basurto Ona X, Rigau Comas D, Urrutia G. Opioids for acute pancreatitis pain. Cochrane Database Syst Rev 2013;7:CD009179.
17 Meng W, Yuan J, Zhang C et al. Parenteral analgesics for pain relief in acute pancreatitis: a systematic review. Pancreatology 2013;13(3):201–206.
18 van Santvoort HC, Besselink MG, de Vries AC et al. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. Ann Surg 2009;250(1):68–75.
19 Li S, Zhang Y, Li M, Xie C, Wu H. Serum albumin, a good indicator of persistent organ failure in acute pancreatitis. BMC Gastroenterol 2017;17(1):59.
20 Shi L, Zhang D, Zhang J. Albumin-bilirubin score is associated with in-hospital mortality in critically ill patients with acute pancreatitis. Eur J Gastroenterol Hepatol 2020;32(8):963–970.
21 Chen L, Huang Y, Yu H et al. The association of parameters of body composition and laboratory markers with the severity of hypertriglyceridemia-induced pancreatitis. Lipids Health Dis 2021;20(1):9.
22 Mounzer R, Langmead CJ, Wu BU et al. Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. Gastroenterology 2012;142(7):1476–1482.
23 Adib-Conquy M, Cavaillon JM. Compensatory anti-inflammatory response syndrome. Thromb Haemost 2009;101(1):36–47.
24 Mao EQ, Tang YQ, Fei J et al. Fluid therapy for severe acute pancreatitis in acute response stage. Chin Med J (Engl) 2009;122(2):169–173.
25 Pinsky MR, Brophy P, Padilla J, Paganini E, Pannu N. Fluid and volume monitoring. Int J Artif Organs 2008;31(2):111–126.
26 Pinsky MR, Teboul JL. Assessment of indices of preload and volume responsiveness. Curr Opin Crit Care 2005;11(3):235–239.
27 Gunn SR, Pinsky MR. Implications of arterial pressure variation in patients in the intensive care unit. Curr Opin Crit Care 2001;7(3):212–217.
28 Zhou F, Mao Z, Zeng X et al. Vasopressors in septic shock: a systematic review and network meta-analysis. Ther Clin Risk Manag 2015;11:1047–1059.

29 Stewart IJ, Sosnov JA, Chung KK. Vasopressin, sepsis, and renal perfusion-a VASST deficit in our understanding. Crit Care Med 2014;42(6):1583–1584.
30 Frat JP, Thille AW, Mercat A et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372(23):2185–2196.
31 The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342(18):1301–1308.
32 Brower RG, Lanken PN, MacIntyre N et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351(4):327–336.
33 Papazian L, Forel JM, Gacouin A et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363(12):1107–1116.
34 Guerin C, Reignier J, Richard JC et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159–2168.
35 Kirkpatrick AW, Roberts DJ, De Waele J et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med 2013;39(7):1190–1206.
36 Navina S, Acharya C, Delany JP et al. Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. Sci Transl Med 2011;3(107):107ra10.
37 de Oliveira C, Khatua B, Noel P et al. Pancreatic triglyceride lipase mediates lipotoxic systemic inflammation. J Clin Invest 2020;130(4):1931–1947.
38 Khatua B, El-Kurdi B, Patel K et al. Adipose saturation reduces lipotoxic systemic inflammation and explains the obesity paradox. Sci Adv 2021;7(5).
39 Nawaz H, Koutroumpakis E, Easler J et al. Elevated serum triglycerides are independently associated with persistent organ failure in acute pancreatitis. Am J Gastroenterol 2015;110(10):1497–1503.
40 Click B, Ketchum AM, Turner R, Whitcomb DC, Papachristou GI, Yadav D. The role of apheresis in hypertriglyceridemia-induced acute pancreatitis: a systematic review. Pancreatology 2015;15(4):313–320.
41 Khatua B, Yaron JR, El-Kurdi B, Kostenko S, Papachristou GI, Singh VP. Ringer's lactate prevents early organ failure by providing extracellular calcium. J Clin Med 2020;9(1).
42 Nair S, Yadav D, Pitchumoni CS. Association of diabetic ketoacidosis and acute pancreatitis: observations in 100 consecutive episodes of DKA. Am J Gastroenterol 2000;95(10):2795–2800.
43 Yadav D, Nair S, Norkus EP, Pitchumoni CS. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. Am J Gastroenterol 2000;95(11):3123–3128.
44 Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. J Clin Gastroenterol 2014;48(3):195–203.
45 Liu M, Gao C. A systematic review and meta-analysis of the effect of total parenteral nutrition and enteral nutrition on the prognosis of patients with acute pancreatitis. Ann Palliat Med 2021;10(10):10779–10788.
46 Al-Omran M, Groof A, Wilke D. Enteral versus parenteral nutrition for acute pancreatitis. Cochrane Database Syst Rev 2003;1:CD002837.
47 Papachristou GI, Muddana V, Yadav D, Whitcomb DC. Increased serum creatinine is associated with pancreatic necrosis in acute pancreatitis. Am J Gastroenterol 2010;105(6):1451–1452.
48 Koutroumpakis E, Wu BU, Bakker OJ et al. Admission hematocrit and rise in blood urea nitrogen at 24 h outperform other laboratory markers in predicting persistent organ failure and pancreatic necrosis in acute pancreatitis: a post hoc analysis of three large prospective databases. Am J Gastroenterol 2015;110(12):1707–1716.
49 Dixit D, Endicott J, Burry L et al. Management of acute alcohol withdrawal syndrome in critically ill patients. Pharmacotherapy 2016;36(7):797–822.