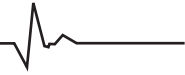# Hepatic, Pancreatic, and Biliary Cancers

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Introduction

The treatment of hepatic, pancreatic, and biliary cancers often leads to life-threatening situations requiring intensive care. For example, hepatectomy or transarterial chemoembolization can cause liver failure, which is best treated in the intensive care unit. Surgery or endoscopic retrograde cholangiopancreatography (ERCP) can lead to pancreatitis and cause septic shock, and ERCP in cholangiocarcinoma may result in cholangitis and septic shock. This chapter will discuss critical care interventions of these and similar side effects of hepatic, pancreatic, and biliary cancer treatments.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer worldwide and the third leading cause of cancer death (Salgia & Singal, 2014). Cirrhosis and the hepatitis C virus (HCV) are the greatest risk factors of HCC development (Bernal & Wendon, 2013). HCV and nonalcoholic steatohepatitis are prominent risk factors in the United States and Europe (Galuppo, Ramaiah, Ponte, & Gedaly, 2014), while the hepatitis B virus is predominantly seen worldwide. Other risk factors include older age, male gender, obesity, diabetes, and alcohol and tobacco abuse (Salgia & Singal, 2014). Treatment for HCC includes resection, locoregional therapies, and chemotherapy (Chung,

2015; Page, Cosgrove, Philosophe, & Pawlik, 2014). Hepatectomy performed in patients of advanced age and with multiple comorbidities increases surgical risk (e.g., extended resections, repeat hepatectomies) (Russell, 2015). Liver failure is a complication after liver resection, and its only treatment is supportive care, which includes treatment to the body systems affected by the failure.

Liver Failure

Postoperative hepatic insufficiency has many surgical and patient risk factors. Prolonged operating room time, excessive blood loss during surgery, extent of resection with a small liver remnant, ischemia, and infection are considered surgical risk factors (Russell, 2015). Patient risk factors include older age, steatosis, fibrosis, cirrhosis, and chemotherapy-induced liver damage (Russell, 2015). Liver insufficiency is defined on postoperative day 3 as a bilirubin level greater than 3 mg/dl. Numerous proposed definitions exist for the criteria of liver failure. An elevated international normalized ratio (INR) and elevated bilirubin on or after postoperative day 5 are widely accepted indicators of liver failure (Russell, 2015).

Neurologic Complications

Hepatic encephalopathy results from portosystemic shunting and hepatocellular dysfunction. Patients with hepatic encephalopathy are at an increased risk of respiratory failure because of ventilation–perfusion mismatch, pulmonary aspiration, acute lung injury, acute respiratory distress syndrome (ARDS), sepsis, pleural effusion, atelectasis, and noncardiogenic pulmonary edema (Al-Khafaji & Huang, 2011; Sargent, 2010). As treatment, lactulose is administered orally or rectally to increase bowel movements (Hansen, Sasaki, & Zucker, 2010). Lactulose acidifies bowel content and slows ammonia absorption, which decreases blood ammonia levels. The goal is to adjust the lactulose to four to five daily bowel movements (Fullwood & Sargent, 2014).

Cardiovascular Complications

Patients with HCC have a dilated vasculature because of splanchnic and peripheral vasodilation, which presents as low blood pressure and high cardiac output (Panackel, Thomas, Sebastian, & Mathai, 2015). Cirrhotic cardiomyopathy is a type of cardiac dysfunction that has impaired contractile responsiveness to stress or altered diastolic relaxation, which prolongs the QT interval. Cirrhotic cardiomyopathy can cause heart failure, renal failure, and ultimately cardiovascular collapse. Once heart failure is present, heart failure management principles are followed as supportive treatment (Al-Khafaji & Huang, 2011).

Impaired sympathetic response causes impaired cardiac contractility with orthostasis and reduced response to vasoconstrictors, requiring careful titration of inotropes and vasopressors. Patients are likely to develop adrenal insuf-

ficiency because of high levels of inflammatory cytokines (Møller & Bendtsen, 2015). IV corticosteroids may be considered when hypotension responds poorly to fluid resuscitation (e.g., isotonic crystalloid and colloid solutions) and vasopressors (Bernal & Wendon, 2013).

Pulmonary Complications

Hepatopulmonary syndrome is the presence of hypoxia caused by ventilation–perfusion mismatch, intrapulmonary shunting, and pulmonary capillary vasodilation (Al-Khafaji & Huang, 2011; Sargent, 2010) and is treated with supplemental oxygen. Patients can develop ARDS from inflammatory cytokines and pulmonary dysfunction. Therapy is supportive, and possible interventions include low tidal volume and high positive end-expiratory pressure (PEEP) (Al-Khafaji & Huang, 2011).

Gastrointestinal Complications

Gastrointestinal bleeding may be a complication of portal hypertension and liver failure. Bleeding can be from gastric and esophageal varices and requires volume resuscitation, blood transfusions, vasoconstrictors, prophylactic antibiotics, and endoscopy. Vitamin K may also be administered (Al-Khafaji & Huang, 2011). Patients with gastrointestinal bleeding are usually intubated to minimize aspiration risk. The aim of variceal bleeding management is to decrease portal pressure with vasopressin and octreotide. Antibiotic prophylaxis for seven days decreases the occurrence of spontaneous bacterial peritonitis (SBP), sepsis, recurrent bleeding, hospital length of stay, and mortality (Al-Khafaji & Huang, 2011).

Hepatorenal Syndrome

Hepatorenal syndrome is an acute kidney injury in patients with liver failure and ascites in the absence of a cause of renal failure. Treatment includes avoidance of nephrotoxins, volume resuscitation, vasoconstrictors, and paracentesis. Albumin may be administered for volume expansion (Al-Khafaji & Huang, 2011). Continuous renal replacement therapy improves the stability of cardiovascular and intracranial function. Bicarbonate-buffered replacement fluid is often used, as the liver is unable to use lactate or acetate to make bicarbonate (Sargent, 2010).

Infection

SBP is the most common infection in patients with liver failure. It can present with no or vague symptoms and can accelerate liver failure. If SBP is suspected, paracentesis should be performed and blood cultures sent (Sargent, 2010). Antibiotic coverage should be directed at gram-negative bacteria, such as *Escherichia coli (E. coli)* and *Klebsiella pneumonia*, and gram-positive cocci, such as *Streptococcus*

and *Enterococcus*. Third-generation cephalosporins are commonly prescribed. A lack of clinical improvement should prompt repeat abdominal imaging and paracentesis (Al-Khafaji & Huang, 2011).

Hyperlactatemia

Lactate production is the result of poor tissue perfusion and anaerobic metabolism. Hyperlactatemia may occur because of poor systemic microcirculation and failure of the liver to clear lactate, leading to hemodynamic instability. High levels of lactate are a predictor of mortality (Sargent, 2010). Treatment of hyperlactatemia should be aggressive and includes appropriate antibiotic use to treat sepsis, adequate systemic oxygen delivery, fluid resuscitation, and avoidance of adrenergic agonists (Suetrong & Walley, 2015).

Hypoglycemia

A high plasma insulin level leads to reduced hepatic uptake and glucogenesis. Glucose infusions are often used to maintain normal blood glucose (Bernal & Wendon, 2013). Daily phosphate, magnesium, and potassium supplementation may be required (Sargent, 2010).

Coagulopathy

Increased consumption of fibrinolytic proteins, anticoagulant proteins, and procoagulant factors with decreased synthesis occurs in liver failure, leading to a prolonged prothrombin time and INR (Sargent, 2010). Stress ulcer prophylaxis with a histamine-2 receptor blocker or a proton pump inhibitor should be implemented to decrease the risk of gastrointestinal bleeding. Fresh frozen plasma should be given for active bleeding for an INR greater than 1.5 for invasive procedures. In patients with a platelet count below 10,000/mm^3, thrombocytopenia is corrected with platelet administration for active bleeding or in invasive procedures (Al-Khafaji & Huang, 2011).

Chemotherapy Side Effects

Sorafenib is the only approved therapy for advanced HCC. It is a multikinase inhibitor with antiprolific and antiangiogenic effects (Galuppo et al., 2014). Side effects typically include hand-foot syndrome and diarrhea (Colagrande, Regini, Taliani, Nardi, & Inghilesi, 2015).

Radiation Side Effects

Radiation-induced liver disease (RILD) creates a venoocclusive disease after conventional radiation therapy (Kimura et al., 2015). Recent advances in radia-

tion techniques provide high radiation doses to focal HCC. Focal radiation therapy has shown injury on imaging to normal and cirrhotic tissue. Stereotactic body radiation therapy and particle therapy have shown no contribution to RILD.

Nursing Implications

Nurses should be aware that hepatic dysfunction can affect the bioavailability of enterally administered drugs through the reduction of the first-pass effect, which involves cytochrome P450. A reduction in the first-pass effect results in a larger amount of the drug reaching the systemic circulation. Common critical care drugs, such as labetalol, metoprolol, midazolam, morphine, nifedipine, and propranolol administered enterally, exhibit increased bioavailability (Lin & Smith, 2010). Delayed gastric emptying may lead to prolonged time for absorption of medications from the small intestine. Diarrhea may limit medication absorption as intestinal transit time increases. The use of vasopressors reduces blood flow to the intestinal tract and absorption of medications (Hansen et al., 2010).

The liver produces albumin, making a low serum albumin level common in patients with liver disease. Medications bound to albumin can result in a high amount of circulating free drug in patients with liver failure, leading to excessive side effects. In the critical care setting, lower doses of medications should be considered, and drug levels should be monitored (Lin & Smith, 2010).

Cholangiocarcinoma

Cholangiocarcinoma is a cancer of the epithelial cells of the biliary tree. The World Health Organization defines two categories of cholangiocarcinoma: intrahepatic (ICC) and extrahepatic (ECC). ECC is further defined as hilar and distal, with hilar accounting for 60%–70% of all cholangiocarcinomas (Kogut, Bastawrous, Padia, & Bhargava, 2013). Surgery is the only potential curative therapy. Biliary obstruction may be a result of tumor progression and requires decompression through stenting of the bile ducts. Decompression of the biliary tree is done via ERCP with stenting. Percutaneous transhepatic cholangiography (PTC) drainage is the treatment for biliary obstruction (Brown, Parmar, & Geller, 2014).

Cholangitis

Acute cholangitis is an infection of the biliary tree. Bile duct obstruction raises the intrabiliary pressure and increases ductal permeability, allowing bacteria into

the vascular system and resulting in bacteremia (Butte, Hameed, & Ball, 2015; Weber et al., 2013). Patients may present with a wide range of symptoms, including severe infection and shock. The Tokyo Guidelines include signs of systemic inflammation (fever), cholestasis, and findings on imaging to define the grade of acute cholangitis (Nishino et al., 2014). Grade I is mild and a diagnosis of exclusion. Grade II is systemic inflammation without organ dysfunction. Grade III is concurrent dysfunction of at least one organ system (Butte et al., 2015).

If acute cholangitis is suspected, the patient should be admitted to the intensive care unit. Typically, crystalloid fluid is given for fluid resuscitation and albumin is given to increase intracellular fluid volume. If mean arterial pressure is less than 65 mm Hg, vasopressive therapy can be initiated. The first therapy choice is norepinephrine with the addition of epinephrine and/or vasopressin. Inotropic therapy with dobutamine can also be used if myocardial dysfunction is noted or in the case of hypoperfusion. Corticosteroids such as hydrocortisone are recommended after fluid resuscitation if vasopressor therapy is unsuccessful (Lee et al., 2013; Lehman & Thiessen, 2015).

E. coli is the normal pathogen in patients with acute cholangitis, but *Enterococcus* and *Klebsiella* species may also be present (Weber et al., 2013). Broad-spectrum penicillin/beta-lactamase inhibitors, such as ampicillin/sulbactam and piperacillin/tazobactam, and third- or fourth-generation cephalosporins are recommended in acute cholangitis (Kogure et al., 2011). Hospital-acquired cholangitis is often caused by multiple resistant organisms, such as vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, and *Pseudomonas* (Mosler, 2011). The type and duration of antibiotic therapy should be based on disease severity. Mild cases should be treated for two to three days, and moderate to severe cases should be treated for at least five to seven days. Ultimately, the patient's clinical picture determines therapy length. Biliary and blood cultures may be used to broaden or narrow the spectrum of antibiotics (Mosler, 2011).

For patients requiring mechanical ventilation with ARDS, a tidal volume of 6 ml/kg of predicted body weight should be targeted with PEEP (Lehman & Thiessen, 2015). Sedation should be minimized, with the patient weaned off as soon as possible.

Overall prognosis of malignancy-causing biliary obstruction is poor. Malignant biliary strictures are managed endoscopically or via percutaneous drainage (Kogut et al., 2013). Patients who have undergone previous endoscopes, have a preexisting sphincterotomy, or have a biliary bypass are at high risk for a superimposed infection. The presence of biliary dilatation or hyperbilirubinemia alone does not indicate that drainage is necessary; however, it may be required to lower bilirubin, enabling the patient to receive chemotherapy.

Chemotherapy Side Effects

Gemcitabine and cisplatin in combination is the standard of care in patients with cholangiocarcinoma (Avan et al., 2015; Lafaro et al., 2015). Sorafenib, erlo-

tinib, lapatinib, panitumumab, cetuximab, sunitinib, and bevacizumab are the targets of the vascular endothelial growth factor involved in angiogenesis and the epidermal growth factor involved in cell proliferation. These have been studied alone or in combination with gemcitabine with no increase in overall survival (Lafaro et al., 2015). Gemcitabine has the potential for pulmonary toxicity with ARDS (Tutar, Buyukoglan, Gülmez, Oymak, & Demir, 2012).

Radiation Side Effects

The role of external beam radiation therapy is controversial in the adjuvant setting and for inoperable ICC (Lafaro et al., 2015). Several small studies have shown improvement in one- and two-year survival with doses greater than or equal to 75 Gy. No radiation side effects have been documented.

Nursing Implications

Biliary drain care is important in preventing recurrent biliary obstruction. Drains should be flushed at least every eight hours or more often if sludge or sediment is present. A change in drainage output or color should be reported to the medical team. The nurse should expect a decrease in total bilirubin with a functioning stent or PTC. The patient should be instructed that the stent will need to be exchanged every six weeks, or sooner if symptoms develop. Symptoms include an inability to flush the drain, fevers, chills, or jaundice, and patients should contact their provider if any of these are present. A patient with PTC drains is usually discharged on antibiotics to prevent recurrent cholangitis. If PTC drains are unable to be internalized because of tumor, the patient should be instructed to maintain hydration above drain output.

Pancreatic Cancer

Pancreatitis

Acute pancreatitis (AP) is an inflammatory disease of the pancreas caused by alcohol, gallstones, hypertriglyceridemia, hypocalcemia, drugs, or after biliary tree manipulation by ERCP (Bolado et al., 2015). Serum lipase and computed tomography of the abdomen and pelvis are recommended to diagnose AP (Yokoe et al., 2015). Magnetic resonance imaging is useful in diagnosing hemorrhagic necrotizing pancreatitis. Tumors causing obstruction of the ampulla, including intraductal papillary mucinous neoplasm, neuroendocrine carcinoma, pancreatic adenocarcinoma, or metastases from other malignancies, have also been associated with AP (Bolado et al., 2015; Yadav & Lowenfels, 2013). AP results in microcirculation disturbances in the pancreatic parenchyma, which can lead to tissue ischemia and cell death (Howard, 2013). This presents as pancreatic and peripan-

creatic necrosis on imaging. Infected pancreatic necrosis can lead to sepsis and death. Close clinical monitoring with aggressive fluid resuscitation and supplemental oxygenation is the basis of supportive care.

AP is divided into two phases. Within the first week of onset, cytokines through the systematic inflammatory response assist in reversible organ failure. A rise in temperature is caused by the autodigestion of the pancreas by pancreatic enzymes. As the patient's condition deteriorates, toxins released by the necrosing pancreas maintain the elevated temperature. Destruction of the capillaries leads to fluid leaking into the abdominal cavity and hypovolemic shock. If the patient is in shock, short-time rapid fluid resuscitation may be used. Permeability of the vessel walls allows bacterial debris to pass to organs, leading to organ failure. Pulmonary edema can occur as fluid shifts across the alveolar–capillary membrane. The focus of treatment for this phase is volume resuscitation with an extracellular solution: Ringer's lactate. Enteral nutrition and treatment of sources of active infection are also part of the treatment plan. Pain is severe and persistent and requires consistent narcotics administration for relief. Death in this phase is attributed to multisystem organ failure (Upchurch, 2014).

The second phase of AP occurs two to four weeks following initial onset. The patient develops systemic sepsis and persistent or new-onset multisystem organ failure. Pancreatic necrosis peaks two to four weeks after onset and is the cause of secondary pancreatic infection with bacterial or fungal organisms (Thandassery et al., 2015). The most commonly found organisms are gram-negative (e.g., *E. coli, Klebsiella, Enterobacter*) and gram-positive (e.g., *Staphylococcus, Streptococcus, Candida*). Targeted antimicrobial therapy is essential. Secondary fungal infection with *Candida* is associated with increased hospital mortality.

Hemodynamic Resuscitation

Cardiovascular and microcirculatory failure in the early stages of AP determines patient outcome. Systemic vasodilation and myocardial dysfunction are also factors contributing to hypotension. Patients may exhibit tachycardia, tachyarrhythmia, weak pulses, cold and mottled skin, and low urine output. Arterial hypotension will develop as a late symptom. The extent of hypovolemia is underestimated, making repeated physical examination and urine output monitoring essential for volume replacement.

Respiratory Treatment

Two time frames exist for the development of pulmonary complications due to AP. On admission, 15% of patients will demonstrate lung injury (Hasibeder, Torgersen, Rieger, & Dünser, 2009). After five days, up to 70% of patients will exhibit acute lung injury (Hasibeder et al., 2009). Acute lung injury is caused by inflammatory changes with leukocyte plugging of capillaries, the formation of pulmonary edema, atelectasis, and reduced chest wall compliance caused by increased intra-abdominal pressure. Symptoms include respiratory

distress, diaphoresis, and anxiety. Mechanical ventilation for lung protection includes PEEP and tidal volumes of 6 ml/kg of ideal body weight. Lung complications in the later phase of AP are associated with pulmonary or extrapulmonary infections.

Intra-Abdominal Hypertension

Body organ edema with ascites formation and distension of intestinal loops increases abdominal pressure and results in vascular compression, reduced venous return, decreased cardiac output, increased arteriolar resistance, and impaired organ blood flow. Tissue hypoxia is aggravated by arterial hypoxia, which results from impaired respirations. Abdominal distension, oliguria, and increased ventricular filling pressures are the first clinical symptoms of intra-abdominal hypertension. Treatment involves gastric decompression, postural changes, sedation, neuromuscular relaxation, and negative fluid balance if possible.

Nutrition

Enteral nutrition within 72 hours of AP reduces infectious complications. Enteral nutrition maintains the integrity of the intestinal barrier, while total parenteral nutrition is associated with a proinflammatory response. Patients with severe shock are likely to develop paralytic ileus and compromised mucosal perfusion. Jejunal enteral feeding into an atonic bowel can cause the intraluminal pressure to exceed the mucosal perfusion pressure, causing ischemia.

Summary

Cancers of the upper gastrointestinal tract and their treatments have the potential to cause life-threatening illnesses, requiring the knowledge and skill of oncology and critical care nurses. Sepsis management is the foundation of care for these critical conditions, including liver failure, acute pancreatitis, and cholangitis. Surviving Sepsis Campaign's 2016 guidelines for managing severe sepsis and septic shock can be viewed at www.survivingsepsis.org/guidelines/pages/default.aspx.

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