Digestive System Disease and Sudden Death

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Abstract

Although sudden death caused by digestive system diseases, accounting for about 7% of sudden death diseases, is not common compared with other diseases such as cardiovascular disease, it is also worthy of attention. Among them, sudden death caused by acute pancreatitis is the most common, accounting for 0.2%-0.5% of natural sudden death, and is one of the important causes of non-cardiac sudden death. This chapter mainly focuses on a series of sudden death related digestive system diseases, including ischemic bowel disease, variceal upper gastrointestinal bleeding in cirrhotic portal hypertension, hepatic encephalopathy, liver failure, acute suppurative cholangitis and acute pancreatitis. This type of disease is characterized by a rapid onset, a rapid progress, and a high mortality rate. Combining typical cases, this chapter describes the pathogenesis, diagnosis and treatment progress of the above-mentioned diseases that may cause sudden death.

Keywords

Digestive system disease · Sudden death · Pathogenesis · Clinical characteristics Diagnosis and treatment progress

23.1 Ischemia Bowel Disease

23.1.1 Introduction

IBD is defined as intestinal ischemic damage caused by insufficient blood supply. It can damage the small intestine, large intestine, or all segments of the intestine. IBD can be divided into chronic mesenteric ischemia (CMI), acute mesenteric ischemia (AMI), and ischemic colitis (IC) [1]. CMI is defined as chronic or persistent hypoperfusion of the bowel due to stenosis or occlusion of the mesenteric artery, also known as intestinal colic [2]. AMI is defined as acute hypoperfusion of the intestine due to obstruction or nonobstructive factors in the mesentery, including mesenteric venous thrombosis, arterial thrombosis, arterial embolism, and nonobstructive ischemia [3]. AMI and CMI are collectively called mesenteric ischemia (MI). IC is also known as colonic ischemia (CI) and defined as reversible or irreversible ischemic damage to the intestinal tract due to decreased colon blood supply. Reversible ischemic damage includes colitis and colon lesions (subepithelial edema or hemorrhage). Colitis usually recovers slowly, and the course of the disease lasts for several months. Colon lesions generally recover within 3 days. Irreversible ischemic damage includes colonic stenosis, gangrene, and fulminant colitis [4]. AMI is extremely susceptible to sudden death and is difficult to diagnose.

23.1.2 Case and Method

A death case occurred in August 2019. We analyzed the death process by reviewing the clinical symptoms, physical examination results, biochemical test results, and clinical treatment medications at the time of death.
A 59-year-old man was admitted to the hospital mainly because of “abdominal pain accompanied by melena for 25 h” with no previous medical history. PE: T 36.8 °C, P 66 cpm, R 22 cpm, BP 121/mmHg, SPO2 97%, clear consciousness, both lungs have rough breathing sounds, no dry or wet rales, HR 78 cmp, irregular S, soft abdomen, total abdominal tenderness, and suspicious rebound pain. CBC: Hb 163 g/L, HCT 0.476 L/L, WBC 13.54 × 10^9 g/L, PLT 121 × 10^9 g/L. CFT: APTT 39.7S, PT 21.5S, TT 12.0S, FIB 7.23 g/L, INR 1.99, D-dimer 6539 ng/mL. BBT: ALT 22.9 U/L, AST 68.1 U/L, TP 57.1 g/L, ALB 28.5 g/L, UREA 11.6 umol/L, CRE 142umol/L. SIM: CRP 27.40 mg/dl and PCT 59.50 ng/mL. This patient was administered hemostatic drugs; gastric acid inhibitors, drugs that inhibit digestive enzymes; antibiotics; and fluid infusion. After 12 h, CTA showed intestinal, colon, and rectal wall thickening, and abnormal lumen of superior mesenteric artery and inferior mesenteric artery. CTA diagnose report showed ischemic bowel disease. Two hours later, the patient was dead because his autonomic heart rate and blood pressure stopped.

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23.1.3 Review and Treatment

23.1.3.1 Etiology and Inducement

The essential pathological basis for this disease was local vascular damage, insufficient blood supply, or hypercoagulability. The major pathological process was intestinal ischemia, hypoxia, and reperfusion. The main pathological feature was a submucosal layer with a large number of hemosiderin cells and fibrous thrombosis. The cause of IBD was unknown; however, it may be related to the following four points: arterial thrombosis, arterial embolism, mesenteric venous thrombosis, and nonocclusive factors. Arterial thrombosis and arterial embolization are called occlusive factors. Previous studies have shown that the risk factors for IBD can be divided into five categories: demographic characteristics, behavioral characteristics, clinical complications, drugs and iatrogenic factors [5]. Demographic characteristics include elderly and female. Behavioral characteristics include smoking, drinking, and strenuous exercise. IBD Patients are usually accompanied by heart failure, arrhythmia, atherosclerosis, diabetes, hypertension, dyslipidemia, irritable bowel syndrome, constipation, chronic obstructive pulmonary disease, and various other symptoms such as shock, arterial thrombosis, mechanical intestinal obstruction, and so on. Iatrogenic factors include aneurysm resection, gynecological surgery, bowel resection, coronary artery bypass surgery, barium enema, colonoscopy, and so on. Drugs commonly used in clinical practice include constipation-causing drugs, narcotic drugs, immunomodulators, nonsteroidal anti-inflammatory drugs, boosters, statins, chemotherapeutics, antibiotics, diuretics, steroid hormones, antipsychotics, cathartic drugs, and so on. Constipation-causing drugs include opioids, alosetron, tricyclic antidepressants, and antidiarrheals. Narcotic drugs include cocaine and amphetamine. Immunomodulators include interferons and tumor necrosis factor inhibitors. Yadav et al. [6] showed that age (>40), gender (male > female), and chronic obstructive pulmonary disease are related to death in patients with CI.
23.1.3.2 Clinical Symptoms
Patients with IBD lack specific clinical signs and symptoms. Their symptoms and signs are not consistent.

Acute mesenteric ischia (AMI) has a rapid onset, a higher mortality, and no specific manifestation at an early stage. The AMI triad is defined as severe upper abdominal pain or umbilical pain without corresponding signs, organic heart disease with atrial fibrillation, and gastrointestinal emptying disorder [7]. The main symptoms of AMI are sudden and severe abdominal pain with frequent vomiting and diarrhea. It has been found that 15–25% of patients with AMI have no symptoms of abdominal pain. They only have unexplained abdominal distension and gastrointestinal bleeding. About 75% of patients have positive fecal occult blood. Bloody stools may occur in 15% of patients. Some patients may have intestinal obstruction. When the patient has severe intestinal ischemia, ulcers and perforations may occur, followed by fever, nausea, vomiting, and signs of peritonitis and sepsis. These factors eventually lead to septic shock.

23.1.3.3 Biochemical Indicators and Imaging Characteristics

Biochemical Indicators
The peripheral white blood cells (WBCs) of patients with IBD are increased. About 75% of patients have WBC >15 × 109 g/L. However, this indicator lacks specificity, and IBD also occurs in patients with normal WBC [8]. It is worth noting that occult blood is often positive in these patients. Alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and creatine kinase (CK) were elevated in patients with IBD. However, the determination of serum enzymes and biochemical indicators also lacks specificity for the diagnosis of AMI. Previous studies have shown that D-lactic acid, L-lactic acid, and intestinal fatty acid binding protein (I-FABP) can increase during intestinal ischemia [9]. D-Lactic acid is an isomer of L-lactic. It is one of the main fermentation products of intestinal bacteria. Normally, D-Lactic acid cannot be absorbed into the blood through the intestinal mucosal barrier. Tissues cannot produce D-lactic acid in the human body. Changes in blood D-lactic acid levels are closely related to intestinal permeability, which can reflect the intestinal barrier function, and are positively related to the degree of intestinal ischemic damage. D-Lactic acid can be used as an early indicator of intestinal ischemia detection, because it has higher specificity than other indicators [10]. Previous animal experiments have found that I-FABP exists in the cytoplasm of cells at the tip of the intestinal villi. Normally, peripheral blood vessels do not contain I-FABP. When intestinal damage occurs, the permeability of intestinal epithelial cells increases, which causes the intestinal villi to release I-FABP into the blood and can be detected in peripheral blood vessels [11]. Kanda et al. [12] found that serum I-FABP levels in patients with IBD were between 20 μg/L and 1496 μg/L, which were significantly higher than normal (<65 μg/L). This indicates that I-FABP has good sensitivity for the diagnosis of IBD. However, due to its poor specificity, complicated detection methods, and high cost, I-FABP is
rarely used in clinical practice. D-Dimer (D-D) is often used clinically as an exclusion test for venous thrombosis. It is an end product of fibrin degradation and an important indicator of thrombosis and embolic disease. Block et al. found that when D-D > 0.9 mg/L, the accuracy of IBD diagnosis is 69%, specificity is 92%, and sensitivity is 60%, and it has a suggestive effect on the progress of the disease. In addition, when D-D > 3.17 mg/L, its sensitivity and specificity can approach that of CT angiography [13].

In addition, interleukin (IL) is a group of soluble proteins with different structures and functions secreted by many types of cells, which participate in the exchange of information between cells. Currently, IL has been found to be of several types including LI-1 to IL-33. Previous studies have showed that IL-6 has a significant upward trend in patients with acute intestinal ischemia [14].

**Abdominal X-Ray Examination**

Abdominal X-ray is the most basic examination of AMI. The most typical sign is the “finger indentation” sign, which can indicate intestinal submucosal edema and bleeding. It should be noted that X-ray examination should not be performed during the period of gastrointestinal bleeding. Barium enema can cause the intestinal spasm. As the disease progresses, the intestinal canal can become stiff like a fence due to submucosal edema and thickening of the folds. In addition, the barium in the intestinal cavity forms a fan-like edge [15]. Barium test can also aggravate intestinal ischemia, which can cause bowel perforation when the patient is seriously ill. Therefore, barium examination is contraindicated in patients with peritoneal irritation. X-ray examination cannot show mesenteric vascular disease, which limits its diagnostic value for MI. On the other hand, a negative result cannot exclude MI.

**Ultrasound Examination**

Ultrasound is a noninvasive imaging examination, which is simple, rapid, and effective. Type-B ultrasonic examination can show mesenteric vascular stenosis and occlusion. The other main signs are as follows: gas accumulation under the diaphragm, thickening of the intestinal wall, gas accumulation in the portal vein and mesenteric vein, and ascites. Ultrasound can be used for screening and identification of IBD. However, it is easily affected by interference factors, such as obese patients, peritoneal effusion, abdominal surgery history, gas accumulation, etc.

**Computed Tomography (CT) Examination**

CT is the best choice for most patients. The reason is that it can comprehensively show the location and extent of lesions and can help identify acute or chronic abdominal pain caused by other causes. By measuring the morphology and inner diameter of blood vessels, nonocclusive mesenteric ischemia can be diagnosed early [16]. Contrast-enhanced CT and CT angiography (CTA) can directly observe the anatomy of the mesenteric artery trunk and its secondary branches, but it is not reliable for assessing branches below the third level [17]. CTA is the preferred test method for diagnosing MI. The sensitivity and specificity for AMI diagnosis are
96% and 94%, respectively [18–20]. However, the disadvantage of CTA is that it is impossible to perform intravascular drug perfusion treatment like intravascular angiography, and it is less sensitive to patients with nonocclusive mesenteric ischemia.

**MRI and MRA**

MRI is similar to CT, but its sensitivity and specificity are low, and it is time-consuming. Therefore, it is generally not used as an emergency examination method. MRA can show mesenteric arterial and venous trunks and their main branches. Its sensitivity and specificity for CMI diagnosis are 100% and 95%, respectively [21]. However, there is a certain false positive rate in the judgment of vascular stenosis. Therefore, it cannot effectively evaluate nonocclusive mesenteric ischemia disease. Overall, MRI is of great value in distinguishing between new and old thrombosis and distinguishing between reversible and irreversible bowel ischemia.

**Angiography**

It is the gold standard for the diagnosis of IBD. In addition, intravascular drug perfusion treatment and interventional treatment can be performed directly during the examination. Studies have shown that the sensitivity of DSA is between 90% and 100%, and the specificity is 100%, which has a significant advantage in the diagnosis of nonocclusive mesenteric ischemia. Application of DSA for diagnosis and treatment can reduce the mortality by 18–53% [1]. Angiography has significant advantages in the diagnosis of nonocclusive mesenteric ischemia. It is therefore the only way to diagnose nonocclusive mesenteric ischemia caused by mesenteric arterial spasm. Patients with severe hypotension and hypovolemia should not use this test. In addition, angiography is not used as a routine test because it is an invasive test method, which is expensive and has related complications.

**Isotope Examination**

Previous studies have shown that scanning techniques for the isotope $^{99m}$Tc and $^{111}$In can show the ischemic area of acute mesenteric occlusion, which can be used as an assisted diagnostic measure for ischemic bowel disease. In patients with ischemic colitis, a colonic scan of white blood cells labeled with the isotope $^{99m}$Tc revealed radionuclide accumulation in the ischemic site of the sigmoid colon. The sigmoid colon formed by it can be used as a diagnostic basis [22]. In addition, research has reported that the albumin-cobalt binding test is a new useful diagnostic indicator for acute intestinal ischemia, with a sensitivity of 100% and a specificity of 85.7% [23].

### 23.1.3.4 Diagnosis

At present, there is no uniform method for the diagnosis of IBD. Clinical diagnosis of patients with IBD needs to be combined with the patient’s medical history, risk factors, clinical manifestations, and auxiliary examinations. IBD needs to be distinguished from gastrointestinal perforation, ulcerative colitis, acute gastroenteritis, Crohn’s disease, acute pancreatitis, and acute appendicitis. According to the standards established by Williams and others, IBD can be diagnosed if it meets the
following six requirements and excludes ulcerative colitis: (1) the acute onset of abdominal pain and blood in the stool; (2) localization of the left colon outside the rectum; (3) no antibiotics; (4) histological biopsy of bacterial culture or fecal examination was negative; (5) colonoscopy manifestations: mucosal congestion, edema, bleeding, and longitudinal ulcer scar (narrow type) in the acute phase, and chronic mucosa to ulcer scar formation in the chronic phase; (6) X-ray examination: thumb indentation sign in the acute phase and transient or narrow ulcer scar in the chronic phase; (7) pathological biopsy: mucosal edema, hemorrhage, necrosis, and protein component exudation in the acute phase, and hemosiderin in the chronic phase. If conditions permit, MRA, angiography, or CTA can be performed in some patients to improve the diagnosis of IBD.

23.1.3.5 Treatment
The treatment of AMI includes medical treatment, interventional treatment, and open surgery. The medical treatment of AMI is as follows: (1) fasting and gastrointestinal decompression if necessary; (2) intravenous nutrition support to correct water and electrolyte balance disorders; (3) correct hypotension, hypovolemia, and arrhythmia; (4) maintain stable blood flow to ensure adequate oxygen supply; (5) early use of broad-spectrum antibiotics to prevent intestinal ischemia from worsening. The antibacterial spectrum should cover aerobic and anaerobic bacteria. Metronidazole and quinolone are commonly used. The third-generation cephalosporins are used in severe infection departments [23, 24]; and (6) adrenal glucocorticoids are used with caution to prevent the spread of necrotic toxins. Once AMI is diagnosed, vasodilators can be applied, and antithrombotic therapy can be initiated early. Aspirin can be given at 200–300 mg/day or clopidogrel t 150–300 mg/day. Patients’ clinical symptoms should be closely observed to prevent bleeding; when patients have mesenteric venous thrombosis, anticoagulation and thrombolytic therapy should be performed. For patients with acute mesenteric arterial thrombosis, early intervention can be used when conditions permit. Interventional treatment includes intra-arterial thrombus removal, implantation of endovascular protectors, percutaneous stent implantation, transcatheter arterial infusion of vasodilators, and thrombolysis. Open surgery includes emergency revascularization, assessment of bowel viability, and removal of necrotic bowel segments, and it is the main treatment for AMI.

23.1.4 Discussion
In the above case, the patient was a middle-aged male who lacked health awareness and could not find that he had atrial fibrillation. He could not accurately report his condition to the doctor, which led to the misleading judgment of gastrointestinal bleeding. Among his biochemical indicators, d-dimer was significantly elevated, suggesting thrombosis. In the case of such patients, combined with their abdominal signs and test results, the doctor usually needs to make a CTA examination in time to rule out the possibility of AMI.
23.1.5 Conclusion

As a type of IBD, AMI is often secondary to patients with atrial fibrillation, and the onset is hidden. It is one of the rarer cases of acute abdomen and is more likely to be missed clinically, so timely diagnosis has a significant impact on the prognosis.

23.2 Variceal Upper Gastrointestinal Bleeding in Cirrhotic Portal Hypertension

23.2.1 Introduction

Portal hypertension is a group clinical syndromes caused by increased portal vein pressure. The most common disease is liver cirrhosis caused by various reasons. The basic pathophysiological characteristics of portal hypertension are obstruction of the portal vein system and (or) increased blood flow, increased static pressure in the portal vein and its branches, and associated collateral circulation. Clinical manifestations are ascites, esophageal and gastric varices (GOV), esophageal and gastric varices rupture and bleeding (EVB), and hepatic encephalopathy [25–27]. EVB has a high mortality rate and is one of the most common digestive emergencies. This article discusses the mechanism and the diagnosis and treatment of sudden death caused by varicose upper gastrointestinal bleeding in cirrhosis through actual cases.

23.2.2 Case and Method

The death occurred in January 2020. We analyzed the death process by reviewing the clinical symptoms, test results, clinical treatment, and medications during the treatment. The sharing of this case has been reviewed by the hospital ethics committee.

Patient Du, male, 49 years old, was admitted to the hospital because of “vomiting blood for 4 h.” He reported dizziness, sweating, fatigue, blurred vision, and other symptoms. He had a history of hepatitis B cirrhosis and diabetes for 6 years. Admission examination: T36.4 °C, P129 times/min, R20 times/min, BP75/45 mmHg, SPO2 98%. Consciousness, pale skin and mucous membranes, normal soft abdomen, tenderness in the upper abdomen, no rebound pain and muscle tension, and no moving dullness. Blood test routine showed Hb 106 g/L, WBC 6.84 × 10⁹ g/L, PLT 60 × 10⁹ g/L. Coagulation function showed APTT 32.5S, PT 18.9S, TT 20.7S, FIB 1.35 g/L, INR 1.74, d-dimer 800 ng/mL. Blood NH3 229.6 umol/L. Biochemical display: ALT 29.4 U/L, AST38.0 U/L, TP 52.8 g/L, ALB 26.9 g/L, GLU13.19 mmol/L, K + 3.35 mmol/L. Abdominal CT showed cirrhosis, splenomegaly, and esophageal and gastric varices. He was observed in the emergency room and immediately given symptomatic treatment such as blood transfusion, fluid replacement, acid production, enzyme inhibition, and so on. He still showed several vomiting symptoms while in hospital, and 7 h later he underwent emergency gastroscopy at the bedside to stop bleeding, but the effect was not good. The patient lost his life after 11 h.
23.2.3 Review and Treatment

23.2.3.1 Etiology and Inducement
Cirrhosis is a common late-stage progression of liver disease with various etiologies. The causes of cirrhosis include viral, alcoholic, cholestatic, circulatory disorders, drug or chemical poisons, genetic and metabolic diseases, immune diseases, parasitic infections, and nutritional disorders [25–27]. Cirrhosis due to any reasons may cause portal hypertension and varicose upper gastrointestinal bleeding [28, 29]. The common predisposing factors include improper diet (eating hard, fried foods, and excessive drinking), emotional instability, fatigue, increased abdominal pressure, and inappropriate medication. Changes in weather and temperature may also be contributing factors.

The risk factors for GOV bleeding include GOV level, red sign, and Child-Pugh classification [26]. Patients without varicose veins or small varicose veins develop varicose veins or develop large varicose veins at a rate of 8% per year. The incidence of varicose vein bleeding is 5–15%, and the mortality rate is as high as 20% within 6 weeks [26, 30–33]. Gastric varices are found in 5–33% of patients with portal hypertension. The incidence of gastric varices bleeding is lower than that of esophageal varices, but the amount of bleeding is often large, the condition is more serious, and the mortality rate can be as high as 45% [34, 35]. Although duodenal varices are rare, varices due to cirrhosis can also occur in upper gastrointestinal bleeding.

23.2.3.2 Lethal Mechanism
Sudden death from varicose veins of the upper gastrointestinal tract due to cirrhosis is related to the following factors:

Hypovolemic Shock
Hypovolemic shock caused by varices and upper gastrointestinal bleeding in cirrhosis is one of the causes of sudden death. The occurrence of hypovolemic shock is related to the amount and speed of blood or body fluid loss. The blood volume is abruptly lost in a short period of time, resulting in a decrease in the cardiac output, which in turn causes tissue cell ischemia, hypoxia, and metabolic disorders.

Septic Shock
Due to the weak intestinal barrier of patients with cirrhosis and portal hypertension, the intestinal flora easily enter the bloodstream and become infected. The peritoneal infection rate in patients with varicose veins and upper gastrointestinal bleeding is 25–65% [36]. Pulmonary infection and abdominal cavity, thoracic cavity, and urinary tract infections can all cause systemic inflammatory response syndrome (SIRS) and severe sepsis and toxic shock from infection.

Multiple Organ Failure (MOF)
Patients with decompensated liver cirrhosis are often accompanied by impairment of the liver, kidneys, heart, and lung function. With varicose upper gastrointestinal bleeding, due to insufficient effective circulating blood volume and reduced coagulation factors, patients can have renal failure, liver failure, and electrolyte and
acid-base balance disorders in a short period of time, and then induce coagulation system and respiratory system and circulatory system failure. Multiple organ failure is undoubtedly one of the additional or contributing factors to sudden death.

**Hepatic Encephalopathy**

Upper gastrointestinal bleeding is one of the important causes of hepatic encephalopathy. In the case of varicose upper gastrointestinal bleeding, the number of ammonia-producing bacteria in the intestine increases, a large amount of bleeding constricts the renal blood vessels, renal urinary dysfunction occurs, urea diffuses into the intestinal cavity, and ammonia production increases. Major blood loss causes hypotension and shock, leading to ischemia and hypoxia in the brain tissue and increased blood–brain barrier permeability. These factors lead to increased blood ammonia. Infection, electrolyte and acid–base imbalance, and the use of sedative drugs can all induce and exacerbate hepatic encephalopathy.

### 23.2.3.3 Diagnosis

Endoscopy is the gold standard for the diagnosis of varicose veins in cirrhosis and their bleeding. Multiple guidelines recommend gastroduodenoscopy (EGD) examinations within 12–24 h of bleeding [25–27, 37, 38]. The diagnosis of esophageal and gastric varicose vein bleeding can be established when the endoscope shows one of the following conditions, such as active bleeding (bleeding and spurting) of varicose veins and no bleeding lesions but obvious veins in other parts. Based on varicose veins, a thrombus head was found, or the surface of varicose veins was covered with blood clots [26].

Laboratory and imaging studies can to some extent determine the presence and severity of esophageal varices. B-ultrasound, CT, MRI, and liver elasticity tests can be used to assist the diagnosis of clinical portal hypertension. Upper gastrointestinal angiography and enhanced CT can also show the presence of gastrointestinal varices [39, 40]. But none of these methods can replace the upper gastrointestinal endoscopy.

The following manifestations suggest that EVB is not controlled: (1) vomiting fresh blood or nasal gastrointestinal aspiration of more than 100 mL of fresh blood ≥2 h after drug or endoscopic treatment and (2) hemorrhagic shock; in the case of no blood transfusion, hemoglobin decreased by 30 g/L during any 24 h period (hematocrit decreased by about 9%). The recurrent clinically significant active bleeding events after bleeding control include vomiting, melena, or blood in the stool; decreased systolic blood pressure > 20 mmHg or increased heart rate > 20 beats/min; and decreased hemoglobin >30 g/L without blood transfusion [38].

### 23.2.3.4 Treatment

The prevention and treatment of EVB includes: (1) prevention of first EVB (primary prevention), (2) control of acute EVB, (3) prevention of secondary EVB (secondary prevention), and (4) improvement of the liver function reserve [34, 35, 38–41]. Here mainly we introduce the treatment of acute active bleeding.
Resuscitation and Medication

1. Supplement blood volume: Resuscitation and maintain hemodynamic stability. Excessive blood transfusion and insufficient blood transfusion can cause damage. Indications for blood volume replenishment: (a) the systolic blood pressure is stable at 90–120 mmHg; (b) pulse <100 beats/min; (c) the urine volume > 40 mL/h and the blood Na+ concentration < 140 mmol/L; and (d) consciousness or improvement, with no obvious signs of dehydration.

2. Use of drugs that reduce the portal pressure: Drug therapy is the preferred treatment. Use vasoconstrictor as early as possible, such as vasopressin or somatostatin, until bleeding is controlled, or continuously use for 5 days. Beta-blockers are contraindicated during acute bleeding. (a) Somatostatin and its analogs including tetradecapeptide (cyclic 14 amino acid peptide, Stannin) and octapeptide (octreotide, Shanning). (b) Vasopressin: it is the strongest visceral vasoconstrictor, which can reduce the blood flow of all internal organs, leading to a decrease in the portal venous blood and a reduction in the portal pressure, but due to higher cardiac and cerebrovascular complications, it is less commonly used. Terlipressin is a synthetic vasopressin analog, which can effectively reduce hepatic venous pressure gradient (HVPG), reduce the portal vein blood flow, and has little effect on systemic hemodynamics.

3. Application of antibiotics: Studies have shown that early re-bleeding and mortality are related to uncontrolled bacterial infections. Antibiotics are recommended to prevent infection.

4. The role of proton pump inhibitors in the treatment of acute varices bleeding is controversial. They are recommended for use with peptic ulcers and can be used as adjuvant treatment after gastric mucosal lesions or endoscopic treatment.

Endoscopic Treatment

Endoscopy is recommended within 12–24 h of bleeding. Patients with severe acute upper gastrointestinal bleeding and unstable disease are advised to undergo endoscopy immediately after resuscitation. Endoscopic treatment is designed to effectively control varicose vein rupture and bleeding, and to minimize or reduce varicose veins to prevent re-bleeding. Preoperative emergency endoscopy preparation for bleeding patients includes routine blood preparation, usually performed in the awake state; patients can be performed on with airway protection (tracheal intubation). Other conditions are similar to those of patients without bleeding. The contraindications of endoscopic treatment: with any contraindication of routine upper gastrointestinal endoscopy.

Endoscopic treatment includes endoscopic variceal ligation (EVL), endoscopic injection sclerotherapy (EIS), and tissue adhesive embolization, with reliable results [38, 42]. Therefore, esophageal and gastric fundus variceal ruptures should be treated with drugs and endoscopic ligation for acute bleeding. The combination of the two is more effective and has fewer complications. (1) EVL and EIS. (a) Indications: acute esophageal varices bleeding, recurrence of esophageal varices after surgery, moderate and severe esophageal varices without bleeding but with a significant risk of bleeding, and a past history of esophageal varices rupture and...
bleeding. (b) Contraindications: those who have contraindications for upper gastrointestinal endoscopy, hemorrhagic shock is not corrected, hepatic encephalopathy ≥ stage II, and excessively large or small varicose veins. (c) Course of treatment: the second ligation treatment is feasible for 10–14 days after the first EVL; the interval between each EIS is 1 week, and it usually takes 3–5 times. The best goal for both treatments is until the varicose veins disappear or almost disappear. (d) Follow-up: it is recommended to review the gastroscopy 1 month after the end of the course of treatment, and then to review the gastroscopy every 6–12 months thereafter. (2) Tissue adhesive treatment. (a) Indications: acute gastric varices bleeding and gastric varices with red signs or surface erosion and a history of bleeding. (b) Method: “Sandwich” method. The total amount is estimated based on the size of the gastric varicose veins, and it is best to occlude the varicose veins once.

After the treatment with drugs or conventional endoscopic ligation or sclerosis, 15–20% of patients still have repeated bleeding or active bleeding that cannot be effectively controlled, and other rescue treatments (such as TIPSS, Surgery) are unable performed, when the patient’s life is seriously threatened, endoscopic esophageal metal stent rescue treatment shows a certain effect.

**Sengstaken-Blakemore Tube**
If bleeding is difficult to control, a Sengstaken-Blakemore tube could be used to stop bleeding until endoscopic treatment, TIPSS, or surgery. It is an important treatment for severe bleeding. Balloon compression can effectively control bleeding, but the re-bleeding rate is high, and it needs to be used in combination with drugs and endoscopic treatment. The complications must be taken seriously, such as aspiration pneumonia, tracheal and esophagus obstruction, gastric mucosa compression, necrosis, and bleeding. The balloon should be deflated once every 8–12 h according to the condition. The extubation timing should follow the principle of the first deflation and then extubation. After the balloon is deflated and left unobserved for 24 h, extubation can be performed.

**Interventional Therapy**
Transjugular intrahepatic portosystem stent shunt (TIPSS) can quickly reduce the portal vein pressure, with an effective hemostatic rate of more than 90%. It has the characteristics of small trauma and low incidence of complications. It is recommended for the “final” treatment of esophageal and gastric fundus varices bleeding, HVPG >20 mmHg and liver function Child-Pugh grade B and C patients with high-risk re-bleeding, and can significantly improve survival [38, 43, 44]. (1) Indications: patients with esophageal and gastric varices rupture and bleeding who were not treated well with drugs and endoscopy, those with varicose veins rupturing and bleeding after surgery, and those with varicose veins rupturing and bleeding while waiting for liver transplantation. (2) Contraindications: Child-Pugh score of liver function >12 points, MELD score > 18 points, PACHE II >20 points, and
irreversible shock status; right heart failure, central venous pressure > 15 mmHg; uncontrollable hepatic encephalopathy; carcinoma located in the first and second hepatic hilum; and intrahepatic and systemic infectious diseases. (3) Others: retrograde varicose vein occlusion under balloon obstruction, splenic artery embolization, percutaneous transhepatic varicose vein embolization, etc.

Surgical Treatment
In about 20% patients, re-bleeding within 24 h after the successfully stopping bleeding. Those who have failed standard medical treatment should be treated with surgery, and portal vein shunt surgery or shunt surgery can be considered [45].

In summary, it is recommended that patients with varicose veins of upper gastrointestinal bleeding in cirrhosis should immediately perform the following treatments: (1) fluid replacement and blood transfusion to correct patients’ hypovolemic shock and stabilize the vital signs; (2) prevent bacterial infection, liver failure, and complications such as renal failure; prevention and treatment of hepatic encephalopathy; (3) pay attention to maintaining airway patency and tracheal intubation if necessary; (4) vasoactive drugs such as somatostatin that reduce varicose vein pressure should be applied immediately, and its analogues like vasopressin; (5) emergency upper gastrointestinal endoscopy and treatment should be performed as soon as possible under the condition of stable vital signs; (6) the treatment method for esophageal varices bleeding is EIS or EVL; EVL For the preferred option; patients with bleeding from varicose veins are preferred to endoscopic tissue adhesive injections. After failure of endoscopic hemostasis treatment, it is recommended to choose: (1) Sengstaken-Blakemore tube; (2) re-endoscopic treatment; (3) transjugular intrahepatic portosystemic stent shunt; and (4) surgery.

23.2.4 Discussion
An important cause of sudden death from upper gastrointestinal bleeding is hemorrhagic shock. In the above case, the patient’s hospital was a teaching hospital and had a complete treatment for upper gastrointestinal bleeding. Patients have typical symptoms of acute blood loss, only 15 h from the onset to death. Except for interventional treatment and surgical treatment, the current treatment schemes for the treatment of upper gastrointestinal bleeding have been implemented, but they have not saved the lives of patients. The main reason for failing to perform interventional treatment is that the patient’s condition has progressed rapidly, and abdominal enhanced CT cannot be performed for preoperative evaluation. Rapid blood loss makes conventional drug hemostasis ineffective, and a large amount of blood entering the intestine breakdown often leading to increased blood ammonia and hepatic encephalopathy. The inability to perform adequate preoperative evaluation is also an important cause of patients’ death. Insufficient blood products and inadequate protection are also one of the reasons.
23.2.5 Conclusion

Sudden death due to upper gastrointestinal bleeding often occurs due to heavy bleeding and delayed treatment. Targeted treatment on the basis of understanding the pathogenesis principle will often achieve more results with less effort. Clinically, cases of upper gastrointestinal bleeding are very common, but cases of sudden death caused by major bleeding are not uncommon and often occur in the emergency room. By understanding the relevant knowledge and principles of upper gastrointestinal bleeding, and choosing a treatment method, we believe that better treatment results will be achieved.

23.3 Hepatic Encephalopathy

23.3.1 Introduction

Hepatic encephalopathy (HE) is a kind of central nervous system dysfunction caused by liver dysfunction and (or) portosystemic stent shunt (PSS), which is based on metabolic disorder. It is manifested as a broad-spectrum neurological or psychological abnormality from reversible subclinical changes to irreversible coma and even death, and other known encephalopathy are excluded. Hepatic encephalopathy is one of the main causes of death in patients with end-stage liver disease, with a mortality rate of more than 50% and poor prognosis. The North American Association for End-Stage Liver Disease Research (NACSELD) has confirmed that HE has an independent correlation with the death of patients with liver cirrhosis. The incidence rate of liver cirrhosis patients complicated with HE is 30–45%, and 40% have mild hepatic encephalopathy (MHE); 30–45% liver cirrhosis patients and 10–50% patients have dominant hepatic encephalopathy (OHE) after transjugular intrahepatic portosystemic shunt (TIPS). In the advanced stage of the disease (liver failure), the incidence and mortality rate of HE gradually increase with the increase of the child Pugh level [46]. This article discusses the mechanism of sudden death caused due to hepatic encephalopathy and its diagnosis and treatment through practical cases.

23.3.2 Case and Method

The death occurred in August 2019. We analyzed the death process by reviewing the clinical symptoms, examination results, test results, and clinical treatment of the death case. The case sharing has been reviewed by the Hospital Ethics Committee.

Patient Deng, a 50-year-old male patient, was hospitalized from 120 because of “defecation of black stool for 8 h and 6 h of sudden disturbance of consciousness.” There was no previous physical examination history, with more than 20 years of drinking history, 250 mL/day. Admission examination: T 36.8 °C, P 170 times/min, R 33 times/min, BP 66/59 mmHg, SPO₂ 92%. Light coma, unable to cooperate with
physical examination, pale skin and mucosa. Blood routine test showed HB 109 g/L, HCT 0.328 L/L, WBC 5.35 × 10⁹ g/L, PLT 73 × 10⁹ g/L. Coagulation function: APTT 36.7 s, PT 21.3 s, TT 20.9 s, FIB 1.61 g/L, INR 1.93, d-Dimer 1210 ng/mL. Blood ammonia 536.4 umol/L. Biochemical indicators: ALT 63.8 U/L, AST 82.0 U/L, TP 61.8 g/L, ALB 25.2 g/L, GLU 9.51 mmol/L, TBIL 59.4 umol/L, DBIL 34.4 umol/L, GGT 108 U/L, UREA 13.0 umol/L, CRE 97 umol/L. Abdominal ultrasound showed cirrhosis, splenomegaly and thickening of the gall bladder wall. The patients were intubated immediately after admission. Immediately endotracheal intubation, ventilator-assisted respiration, and symptomatic treatment such as reducing blood ammonia, boosting blood pressure, stopping bleeding, inhibiting acid, inhibiting enzyme, anti-infection, fluid replacement, etc., were given. After 10 h, the patient’s heart rate and blood pressure could not be maintained and he lost his life.

23.3.3 Review and Treatment

23.3.3.1 Etiology and Inducement

The main causes of hepatic encephalopathy are liver cirrhosis, abnormal portosystemic shunt, and other metabolic abnormalities caused by chronic liver disease. The causes of cirrhosis include chronic hepatitis B and C, alcoholic liver disease, drug-induced liver disease, autoimmune liver disease, and schistosomiasis; portosystemic shunt mainly includes hepatic vascular lesions such as Budd–Chiari syndrome, idiopathic portal hypertension, and portal hypertension after TIPS; metabolic abnormalities often include chronic liver damage caused by copper metabolism, iron metabolism, porphyrin metabolism disorders, and congenital urea circulation disorders. Other causes include severe hepatitis, fulminant liver failure, primary liver cancer, biliary tract diseases, acute fatty liver in pregnancy, etc. Common inducing factors include application of infection, gastrointestinal hemorrhage, ascite discharge, electrolyte disturbance, massive potassium drainage diuresis, high protein diet, constipation, hypnosis and sedation, anesthetics, uremia, surgery, proton pump inhibitors, etc. Among them, infection is the most common inducing factor, including abdominal cavity, intestinal tract, respiratory tract, and urinary tract infection, and abdominal infection is the most important. The occurrence of MHE has no obvious correlation with the etiology, but its incidence and mortality increase with the aggravation of the decompensation degree of liver cirrhosis.

23.3.3.2 Pathogenesis and Lethal Mechanism

The pathogenesis and death mechanism of hepatic encephalopathy are not completely defined. Brain edema and astrocyte changes are the main pathological features. At present, there is no single theory that can explain the occurrence and death of HE, which may be related to the following theories and mechanisms [47–49]:

Ammonia intoxication hypothesis is the main pathogenesis of hepatic encephalopathy. The basis of the ammonia intoxication theory is that impaired astrocyte participates in the occurrence and development of hepatic encephalopathy. (1)
Inadequate ammonia clearance: in cirrhosis with portal hypertension, the detoxification function of liver cell dysfunction to ammonia and other toxic substances is reduced, the circulation of ornithine is blocked, and the process of ammonia to urea is disturbed. (2) Increased ammonia production: portal-integrated circulation shunting enables a large amount of toxic substances such as ammonia being absorbed into the blood by the intestinal tract to directly flow into human circulation through portal vein. Intestinal dysfunction increases the retention of nonabsorbed protein components in the intestinal tract. Active intestinal bacteria can release amino acid oxidase and urease, increasing ammonia production, especially during gastrointestinal hemorrhage and intestinal infection. Increased intestinal permeability can lead to the increase of ammonia in the portal vein. When kidney involvement alkalosis occurs, the hydrogen ion excretion in the renal tubules is reduced, the generation of ammonia ions decreases, and ammonia increases. In patients with hepatic encephalopathy, restlessness and muscle tremor increase adeny late decomposition, and cause an increase in ammonia production. (3) Toxic effects of ammonia on the brain: increased permeability of the blood–brain barrier; blood ammonia entering the brain tissue increases glutamine synthesis by astrocytes, leading to degeneration, swelling, and degeneration of astrocytes and neuron cells. As a result, brain edema and acute neurocognitive dysfunction are formed. Ammonia directly leads to imbalance of excitatory and inhibitory neurotransmitters, reduction of excitatory neurotransmitters such as acetylcholine, and enhancement of inhibitory neuron activity. The enhancement of inhibitory neuron activity increases inhibitory neurotransmitters such as glutamine and GABA, which impair the automatic regulation of intracranial blood flow. The increased ammonia interferes with the tricarboxylic acid cycle of the brain cell energy metabolism and affect the function of the nerve cell membranes, thus causing disorder in the excitatory activity of the central nervous system. In addition, ammonia can directly damage the electrical activity of nerves. In summary, the damage to the central nervous system caused by the increase of ammonia can cause the disease to rapidly progress into irreversible coma and death [50–52].

Damage of Inflammatory Mediators
The interaction between hyperammonemia and inflammatory mediators promotes the occurrence and development of HE. Inflammatory mediators can lead to the destruction of the blood–brain barrier, thus allowing toxic substances such as ammonia and inflammatory cytokines to enter the brain tissue, causing changes in brain parenchyma and brain dysfunction. Hyperammonemia can induce neutrophil dysfunction to release reactive oxygen species, which promote the body to produce oxidative stress and inflammatory response. Cytokines produced in the process of the inflammatory reaction in turn aggravate liver injury and increase HE. This forms a vicious circle.

Enterogenous Endotoxemia and Flora Disorder
Endotoxin level in patients with severe liver diseases are significantly increased, which is parallel to the degree of liver damage and reciprocal cause and effect each
other with liver damage. Clinical observation shows that endotoxin in liver disease patients is correlated with the occurrence of hepatic encephalopathy, renal failure, hemorrhagic nephritis, and DIC. The mechanism of enterogenous endotoxemia [53]: (1) increased absorption of endotoxin—disturbance of intestinal flora, abnormal increase of bacteria, destruction or increase of the permeability of intestinal mucosa and vascular integrity, weakening of the intestinal mucosal barrier function, bilirubin and bile acid inhibiting phagocytosis of Kupffer cells caused by intrahepatic cholestasis, decrease of intestinal liner salt when bile excretion is blocked, etc. can lead to increase in the absorption of intestinal endotoxins; (2) dysfunction of endotoxin clearance: intestinal endotoxemia caused by dysfunction of Kupffer cells plays a decisive role in the induction of severe liver disease. When the liver function is incomplete, with the damage of hepatocytes, Kupffer cells and their peripheral cells change from the activated state to failure and their function is seriously damaged, and the scavenging effect of endotoxin is obviously weakened. Some studies have shown that the endotoxin level in patients with hepatic encephalopathy is significantly increased, and is positively correlated with the severity of hepatic encephalopathy, but the specific pathological mechanism has not been clearly explained.

**Dysfunction of the Brainstem Reticular System**

Neuronal activity of the brainstem reticular system and the nigrostriatal system in patients with severe cirrhosis is damaged to varying degrees, leading to the occurrence of HE, flapping wing-like tremor, and changes in muscle tone. In addition, the increase of pseudoneurotransmitters makes the wake-up function of the ascending activation system of the brainstem reticular structure unable to be maintained, resulting in coma. The damage degree of the brainstem reticular system is consistent with the severity of HE [54].

**Manganese Poisoning Theory**

In liver diseases, the manganese that is out of control enters the nerve cell, and generates low-valence manganese ions to be oxidized into high-valence manganese ions, which accumulate in the mitochondria through the specific affinity of manganese to the mitochondria and directly damage the brain tissue. At the same time, manganese ions generate a large number of free radicals during the valence state transition process, which leads to decreased activity of key enzymes in the respiratory chain of the mitochondria in the brain substantia nigra and striatum. Manganese can also affect the functions of 5-HT, norepinephrine, GABA, and other neurotransmitters, causing astrocyte dysfunction [55].

**Amino Acid Imbalance, Inhibitory Neurotransmitter, and Pseudoneurotransmitter Theory**

When liver function is damaged, the ability to degrade aromatic amino acids is reduced, and phenylalanine and tyrosine in the blood are increased, thus inhibiting the production of normal neurotransmitters. Increased levels of phenylalanine and tyrosine produce phenylethanolamine and hydroxyphenylethanolamine, known as pseudoneurotransmitters, which replace the normal neurotransmitter and lead to HE.
GABA (Gamma-Aminobutyric Acid)
It is a unique and main inhibitory neurotransmitter in the central nervous system. It exists in the form of compound receptors with benzodiazepine receptors in the brain. The content of GABA in the blood increases in HE, and the amount of GABA passing through the blood–brain barrier is increased, so that the level of endogenous benzodiazepine in the brain is increased.

Cerebral Edema and Stroke
All of the above mechanisms can lead to cerebral edema and neuroastrocytic lesions, which can cause irreversible damage to the nervous system, and even lead to sudden death due to cerebral hemorrhage, cerebral infarction, brain hernia, and other stroke [54].

Other lethal mechanisms: Infection and septic shock, respiratory failure, malignant arrhythmia, and hepatic encephalopathy are the leading causes of death in severe liver disease. Infection can induce hepatic encephalopathy, which aggravates primary liver disease. In addition, patients with hepatic encephalopathy are bedridden for a long time and have low immunity, which is extremely easy to promote exacerbation of infection and even septic shock. End-stage liver disease itself can cause hepatopulmonary syndrome and respiratory system damage; when complicated with hepatic encephalopathy, central nervous system involvement also affects the respiratory function, both of which aggravate respiratory system damage and eventually lead to respiratory failure. Various electrolyte disorders (hyponatremia) and acid–base imbalance complicated with hepatic encephalopathy can lead to malignant arrhythmia and even sudden cardiac death.

23.3.3.3 Diagnosis
Compared with other metabolic encephalopathy, the clinical manifestations of hepatic encephalopathy are not specific. It emphasizes clinical diagnosis based on severe liver disease or (and) portosystemic shunt and underlying diseases with related inducements, combined with clinical and related auxiliary examinations.

Clinical manifestations of HE are mainly the dysfunction of the higher nerve center (personality change, mental decline, abnormal behavior, and disturbance of consciousness) and abnormal movement and reflex (such as flapping-wing tremor, myoclonus, hyperreflexia and pathological reflex). At present, the West-Haven classification standard is mostly adopted to divide hepatic encephalopathy into five stages [56]:

- Stage 0 (incubation period): That is, minimal hepatic encephalopathy, no abnormal behavior and personality, no neurological and pathological signs, and normal electroencephalogram, but only the psychological test or intelligence test shows a slight abnormality.
- Stage 1 (prodromal period): Mild personality changes and mental abnormalities, such as anxiety, euphoric excitement, apathy, sleep inversion, amnesia, etc., may have flapping-wing tremor; EEG is mostly normal. The clinical manifestations at this stage are not obvious and are easy to be ignored.
- Stage 2 (pre coma period): Sleepiness, abnormal behavior, slurred speech, dysgraphia, and disorientation. Neurological signs such as hypertonia, hyperreflexia,
ankle clonus, and Babinski sign are positive; flapping-wing tremor is positive, and electroencephalogram shows characteristic abnormalities.

- **Stage 3 (lethargy period):** Sleepiness but wakefulness, response when awake, unconsciousness or hallucination, continuous or aggravating of various neurological signs, positive flapping-wing tremor, increased muscular tension, and hyperreflexia of tendon reflex. Pyramidal sign often is positive, and electroencephalogram has abnormal waveform.

- **Stage 4 (coma period):** Coma and unable to wake up. Cannot cooperate with physical examination, and cannot lead to flapping wing tremor. In shallow coma, tendon reflex and muscle tension are still hypertonic. In deep coma, all kinds of reflexes disappear and muscle tension decreases. The electroencephalogram is obviously abnormal.

**Auxiliary Examination**

*Laboratory examination:* Elevated blood ammonia is of high value in the diagnosis of HE, especially in patients of HE with portal-systemic shunting, most of whose blood ammonia is increased. The elevated level of blood ammonia is not completely consistent with the severity of the disease, and sometimes patients with normal blood ammonia cannot be excluded from HE. Biochemical indexes such as bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, prothrombin activity, renal function, and blood routine test were all used as routine laboratory indicators when HE was suspected. Other laboratory indicators: serum chitinase-3 like protein 1 (CHI3L1), a member of the glycosylase hydrolase family, is a protein secreted in the extracellular matrix by the liver. Its expression is significantly increased during cirrhosis and liver fibrosis, and the expression level of CHI3L1 reflects the degree of cirrhosis and liver fibrosis. Golgi protein 73 (GP73) is a transmembrane glycoprotein located in the Golgi body. In advanced liver disease caused by various causes, the expression level of GP73 in liver cells is increased.

*Neuropsychological test:* (1) Traditional paper–pen neuropsychological test includes the digital connection test (NCTA and B), the digit-symbol test (DST), the line-tracing test (LTT), and the serial dotting test (SDT); five subtests of the series dotting test. NCT and DST are simple and easy to operate, with strong operability, and are suitable for epidemiological investigation of MHE. MHE can be diagnosed if both NCT-A and DST are positive, or if any two of the five subtests are abnormal. (2) Critical flicker frequency (CFF): CFF is the minimum stimulus frequency that can cause flash fusion sensation, and it reflects brain nerve conduction dysfunction. It has moderate sensitivity and high specificity. CFF is an auxiliary inspection means, which is easy to interpret when used for diagnosing MHE. (3) New neuropsychological testing methods: animal naming test (ANT), gesture control and stability test, multi-sensory integration test, etc. (4) Others: repeatable battery for the assessment of neuropsychologic status (RBANS): it is one of the two neuropsychological examination tools recommended by ISHEN’s guidelines, including Stroop and Encephal APP test, inhibitory control test (ICT), SCAN test, etc.

*Neurophysiological test:* The abnormality of electroencephalogram is mainly manifested by slow rhythm, which is not a specific change of HE, and typical electroencephalogram changes can only be detected in patients with severe HE, so it is
only clinically used for auxiliary diagnosis of HE in children. Evoked potential detection, includes visual evoked potential, auditory evoked potential, and somatic evoked potential, among which endogenous time-related evoked potential P300 has the best sensitivity. And the MHE patients can show prolonged latency and reduced amplitude. The advantage of neurophysiological examination is that the result is relatively specific and there is no learning effect. Its shortcomings are poor sensitivity, the need for professional equipment and personnel, and poor consistency with neuropsychological test results.

*Imaging examination*: CT scan of the liver and brain can determine whether there is obvious portosystemic shunt, find brain edema, and exclude cerebrovascular accidents and intracranial tumors. MRI showed normal white matter area in patients with liver cirrhosis complicated with HE, but the mean diffusivity degree (MD) could still be significantly increased, which was related to HE staging, blood ammonia, neurophysiology, and neuropsychological changes. Functional magnetic resonance imaging (fMRI): resting fMRI analyzed by ReHo analysis can be used as a noninvasive examination method, which has an important value in revealing the cognitive changes of patients with cirrhosis [52].

### 23.3.3.4 Classification of Hepatic Encephalopathy

*Classification according to the basic liver disease*: Hepatic encephalopathy was classified as type A, type B, and type C at the 11th Vienna WCOG in 1998 (Table 23.1). Type A develops rapidly on the basis of acute liver failure, and its pathophysiological characteristics are cerebral edema and intracranial hypertension. Type B is caused by portosystemic shunt without obvious liver dysfunction, and liver histopathological examination (liver biopsy) indicates a normal liver histologic structure. Type C is hepatic encephalopathy associated with liver cirrhosis, accompanied by portosystemic venous shunting, with manifestations of chronic liver injury, liver cirrhosis, and other liver-based diseases. Clinically, HE caused by liver cirrhosis is the most common type, that is, type C. At the same time, hepatic

| Type of hepatic encephalopathy | Definition                                      | Subclass | Subtype       |
|--------------------------------|------------------------------------------------|----------|---------------|
| Type A                         | Associated with acute liver failure             | No       | No            |
| Type B                         | Portal-systemic shunt related                   | No       | No            |
| Type C                         | Associated with liver cirrhosis complicated with portal hypertension or portal-systemic shunt | Episodic | Precipitated  |
|                                |                                                |          | Spontaneous   |
|                                |                                                |          | Recurrent     |
|                                |                                                | Persistent | Mild         |
|                                |                                                |           | Severe        |
|                                |                                                | Treatment dependent | No |

*Table 23.1* Classification of hepatic encephalopathy recommended by the 11th World Congress of Gastroenterology (Vienna, 1998)
encephalopathy of type C can be further divided into paroxysmal type, persistent type, and mild type [57, 58].

Class**Classification by severity:** ISHEN established a grading standard called SONIC according to the severity of hepatic encephalopathy. Hepatic encephalopathy of grade I in MHE and West-Haven grades is classified as Covert HE (CHE), in which minimal hepatic encephalopathy (MHE) refers to hepatic encephalopathy that is usually found only through neuropsychological tests without obvious clinical symptoms. Overt hepatic encephalopathy (OHE) is a type of hepatic encephalopathy diagnosed by clinical standards, including hepatic encephalopathy of grade 2 and above [59].

**23.3.3.5 Diagnostic Criteria**

**OHE:** According to clinical manifestations and signs and West—Haven grading standards, OHE diagnosis is not difficult, and neuropsychological, neurophysiological, and imaging examinations are generally not required. Key points of diagnosis: (1) there are basic diseases that cause HE, such as severe liver diseases and/or extensive portosystemic collateral circulation shunts; (2) clinically identifiable neuropsychiatric symptoms and signs; (3) excluding other diseases causing neuropsychiatric abnormalities, such as metabolic encephalopathy, toxic encephalopathy, neurological diseases (such as intracranial hemorrhage, intracranial infection, and intracranial space occupying), psychiatric diseases, etc.; (4) paying special attention to find out the inducement of HE (type C and type B), such as infection, upper gastrointestinal hemorrhage, massive ascites, etc.; and (5) blood ammonia increase.

**MHE:** Because patients have no obvious abnormal cognitive function, special examination is often needed to make a definite diagnosis, which is the focus of clinical attention. MHE can be diagnosed if it meets any one or more of the following main diagnosis points (1), (2), and (3–6). Main diagnostic points: (1) there are basic diseases causing HE, that is severe liver disease and/or extensive portosystemic collateral circulation shunt. (2) At least two abnormalities in traditional neuropsychological test indicators. (3) In the new neuropsychological test method (ANT, posture control and stability test, and multi-sensory integration test), there should be at least one abnormality; (4) abnormal CFF detection; (5) abnormal EEG, visual evoked potential (VEP), and brainstem auditory evoked potential (BAEP); and (6) fMRI abnormality.

**23.3.3.6 Differential Diagnosis**

HE should be distinguished from the following diseases: (1) mental disorders; (2) intracranial lesions; (3) other metabolic encephalopathy, including ketoacidosis, hypoglycemia, hyponatremia, renal encephalopathy, pulmonary encephalopathy, etc.; (4) Wernicke encephalopathy; (5) toxic encephalopathy, including alcoholic encephalopathy, acute poisoning, withdrawal syndrome, heavy metal (mercury, manganese, etc.) encephalopathy, and toxic reactions of psychotropic drugs or salicylate drugs, etc.; (6) Parkinson’s disease related to cirrhosis; (7) hepatic myelopathy; and (8) acquired liver and brain degeneration, etc.
23.3.3.7 Treatment

Treatment principles: Clearing the inducement in time, treating the primary liver disease actively, maintaining the balance of liver function, promoting the clearance of ammonia metabolism, regulating neurotransmitters, restoring the acute neuropsychiatric disorder to the baseline state as soon as possible, and primary prevention and secondary prevention.

Remove the Inducement of MHE/HE

(1) Preventing and controlling infection: Since infection is the most common inducing factor, we should actively search for the source of infection and start using empirical antibacterial drugs as early as possible: even if there is no clear infection site, there is also a potential inflammatory state due to intestinal bacterial translocation and increased endotoxin level, and antibacterial treatment can reduce this inflammatory state. (2) Hemostasis and removal of intestinal hematomele: gastrointestinal bleeding is also a common inducing factor of HE, so bleeding should be stopped as soon as possible, and hematomele in the gastrointestinal tract should be removed. Meanwhile, intestinal tract should be acidified and stool should be kept normally. (3) Correcting electrolyte disorders (hypokalemia or hyperkalemia, hyponatremia or hypernatremia): alkalois and electrolyte disorders related to insufficient effective circulation volume caused by excessive diuresis can induce HE, and in this case, it is necessary to suspend diuretics and supplement liquid and albumin. Hypovolemic hyponatremia (especially sodium lower than 110 mmol/L) should be supplemented with normal saline intravenously, while selective vasopressin type 2 receptor (V2) antagonist can be used for hyponatremia patients with high or equal volume. For patients with HE in grade 3–4, cerebral edema should be actively controlled and 20% mannitol or furosemide should be given. (4) Use sedative drugs and liver injury drugs with caution: sedative, hypnotic, analgesic drugs, and anesthetics can induce hepatic encephalopathy and should be avoided as much as possible. Some studies have shown that propofol can control the manic symptoms of HE more safely and effectively.

Treatment of Primary Liver Disease

(1) Improving liver function: Strengthening liver protection, promoting liver metabolism, reducing liver inflammatory response, etc. (2) Interrupting portosystemic shunting. (3) Artificial liver: it can remove some inflammatory factors, endotoxin, blood ammonia, bilirubin, etc., to a certain extent. The artificial liver modes commonly used to improve hepatic encephalopathy include hemoperfusion, hemofiltration, plasma filtration dialysis, molecular adsorption recirculation system (MARS), dual plasma molecular adsorption system (DPMAS) or plasma exchange combined hemoperfusion, etc., especially to relieve liver failure and preparation for liver transplantation. (4) Liver transplantation.

Promote ammonia metabolism and reduce the generation and absorption of enterogenous toxins. Hyperammonemia is one of the important factors in the occurrence of hepatic encephalopathy, so it is very important to reduce the generation and
absorption of ammonia [60]. The main drugs for reducing blood ammonia are: (1) Lactulose: mainly reduce ammonia absorption and promote ammonia excretion by reducing pH value in intestinal tract, retaining water in intestinal tract and increasing stool volume, stimulating colon peristalsis, defecating smoothly, catharsis, restoring physiological rhythm of colon, promoting growth of intestinal acidophilic bacteria (such as lactobacillus), inhibiting proteolytic bacteria, reducing translocation of intestinal bacteria, transforming ammonia into the ionic state, etc., to improve hepatic encephalopathy. Take 15–30 mL orally each time, 2–3 times/day (adjust the dose according to the patient’s reaction), with soft stool 2–3 times a day is appropriate. If necessary, it can be combined with retention enema. (2) Lactitol: the recommended initial dose of lactitol is 0.6 g/kg, which is taken three meal times, and the dosage is increased or decreased according to the standard of defecation twice a day. The principles of action and effect are the same as lactulose, which has the advantages of a fast onset of action, low incidence of abdominal distension, and low sweetness, and can be applied to diabetic patients. (3) LOLA: the dosage is 10–40 g/d, intravenous drip. LOLA promotes the utilization of ammonia in the brain and kidneys by promoting the circulation of ornithine in the liver and the synthesis of glutamine, thus consuming ammonia to synthesize glutamic acid and glutamine. LOLA can also reduce fasting blood ammonia and postprandial blood ammonia and reduce cerebral edema. (4) Rifaximin [61]: the dosage is 800–1200 mg/day, and is taken orally for 3–4 times. Theoretically, rifaximin can reduce the absorption of ammonia in intestinal tract, but its clinical effect is not good, especially for type B hepatic encephalopathy. (5) Microecological preparations [62, 63]: including probiotics, prebiotics, synbiotics, etc. It alleviates intestinal endotoxemia by promoting the growth of intestinal probiotic strains, inhibiting the growth of harmful flora, improving the nutritional status of intestinal epithelial cells, reducing the permeability of intestinal mucosa, and reducing bacterial translocation. It can also reduce inflammation and oxidative stress of liver cells, thereby increasing ammonia clearance of the liver.

Regulating neurotransmitters like arginine, glutamine, and branched chain amino acids is used clinically to competitively inhibit aromatic amino acids from entering the brain and reduce the formation of pseudoneurotransmitters [64].

Nutritional support therapy: The recommended daily ideal energy intake is 35–40 kcal/kg (1 kcal = 4.184 kJ), less food and more meals, add meals before bed (including at least 50 g of compound carbohydrates), and the fasting time in day time should not exceed 3–6 h. (1) Protein: the European society for parenteral nutrition guidelines recommended that the daily protein intake is 1.2–1.5 g/kg to maintain nitrogen balance. Daily dietary protein intake of obese or overweight liver cirrhosis patients is maintained at 2 g/kg. Patients with recurrent/persistent HE should take 30–40 g vegetable protein daily. Protein supplementation for HE patients should follow the following principles: it is forbidden to supplement protein from intestinal tract for patients with HE grade 3–4. Patients with MHE and L to 2 grade HE should limit the amount of protein to 20 g/day in the first few days. With the improvement of symptoms, 10–20 g protein can
be added every 2–3 days. Plant protein is superior to animal protein. It is safe to supplement albumin intravenously. For patients with chronic HE, it is encouraged to have more meals a day but less food at each, and gradually increase the total amount of protein. The protein intake should be individualized. (2) Branched chain amino acid (BCAA): patients with grade 3–4 HE should be supplemented with parenteral nutrition preparations rich in BCAA (valine, leucine, and isoleucine). (3) Other micronutrients: trace elements and water-soluble vitamins, especially thiamine and zinc element. A multivitamin or zinc supplement may be replenished.

23.3.3.8 Prevention

**Primary prevention**: Treatment of primary liver diseases and nutritional intervention. Etiological treatment can reduce injury and liver fibrosis from liver inflammatory, reduce pressure of portal vein, and prevent liver cirrhosis from progressing or reversing liver cirrhosis, which is of great significance in preventing and controlling the occurrence of HE and other complications. The main treatment measures include active prevention and treatment of infection, gastrointestinal hemorrhage, electrolyte disturbance, acid-base imbalance, constipation, and other inducing factors of HE; avoiding excessive diuresis and releasing a large amount of ascites; having more meals a day but less food at each; and avoiding excessive high protein diet.

**Secondary prevention**: The emphasis is on health education for patients and their families, control of elevated blood ammonia, and regulation of intestinal microecology. The patient should adjust the diet structure reasonably according to the liver function injury under the guidance of the doctor, and avoid taking a large amount of high protein diet at one time during the attack of hepatic encephalopathy. Lactulose and lactitol can be used as preventive drugs. Gradually guide the patient’s self-health management, and guide the patient’s family members to pay attention to the patient’s behavior and personality changes, and at the same time, closely inspect whether the patient has loss of attention, memory, and orientation so as to achieve early detection, early diagnosis, and early treatment of HE as much as possible.

23.3.3.9 Prognosis

Patients with mild hepatic encephalopathy can be relieved after active treatment. It will quickly progress to coma or even death in hepatic encephalopathy with no obvious inducement caused by acute liver failure. The inducement of hepatic encephalopathy on the basis of decompensated cirrhosis is clear, and the disease can be recovered and improved by actively removing the inducement and treating the primary disease. Patients with better liver function, after shunt operation and definite inducement, usually have better prognosis. Patients with hepatic encephalopathy on the basis of the end stage of liver cirrhosis suffer from slow progress, repeated attacks, gradual progress, poor prognosis, and rapid death without liver transplantation. Hepatic encephalopathy caused by fulminant liver failure has the worst prognosis.
23.3.4 Discussion

In the above cases, the patient is a middle-aged male, has a long history of drinking alcohol, lacks health awareness, and is unaware of the progression of his disease to liver cirrhosis. The lethal mechanism of hepatic encephalopathy has not yet been determined by the medical community, and the classification of hepatic encephalopathy has also produced a variety of standards due to different diagnostic methods. In this case, hepatic encephalopathy is a secondary change of varicose upper gastrointestinal hemorrhage in liver cirrhosis, and the very high blood ammonia concentration of the patient is extremely significant for brain damage. Usually, during gastrointestinal hemorrhage, ammonia is usually separated from the blood in the digestive tract and absorbed into the blood through the intestinal tract, resulting in high blood ammonia.

Although modern medicine has studied many methods to reduce the concentration of blood ammonia, there is a lack of faster and better methods to reduce the concentration of blood ammonia due to the lack of a clear understanding of its pathogenesis.

23.3.5 Conclusion

Through specific cases, we understand the harm of hepatic encephalopathy to the human body and also understand the methods of treating hepatic encephalopathy. However, these are no means that can be used once and for all. Lack of treatment measures to rapidly reduce the blood ammonia concentration is one of the biggest problems in the treatment of hepatic encephalopathy. We hope to find better treatment methods and save more patients by summarizing the past experience and exploring new things.

23.4 Liver Failure

23.4.1 Introduction

Liver failure refers to severe liver damage caused by various factors (virus, alcohol, drugs, etc.), resulting in a large number of liver cell necrosis, leading to severe dysfunction or decompensation of liver metabolism, synthesis, detoxification, secretion, biotransformation, immune defense, and other functions, and then form a group of clinical syndromes with coagulation mechanism disorders, jaundice, hepatic encephalopathy, ascites, and other main manifestations. Liver and coagulation failure gradually progress to multiple organ failure which may include nervous, circulatory, respiratory, and renal system. Liver failure may cause short time death or even sudden death. The survival rate of patients with liver failure is only 20–40% who were treated with comprehensive treatment. The mortality rate is very high and increased with other organ injuries involved. This article discusses the mechanism
of death caused by liver failure and the diagnosis and treatment through practical cases.

The death occurred in August 2019. We respectively collected the clinical symptoms, lab results, and treatment to analyze the course of death. Sharing this case was approved by the hospital ethics committee.

23.4.2 Case and Method

Patient Zheng, male, 49 years old, was admitted to the hospital mainly because of “liver occupation for 2 months, hematemesis and black stool for more than 10 h.” Due to the large amount of ascites and the space occupation throughout the liver and portal vein, he failed to take an active anti-tumor treatment program. This patient has no previous physical examination history. He has a drinking history of more than 30 years, about 150 mL/day. Physical examination on admission: T 36.6 °C, P 72 times/min, R 24 times/min, BP 91/57 mmHg, SPO₂ 97%. Consciousness, with yellow skin and mucous membrane. Blood routine test showed Hb 103 g/L, HCT 281 L/L, WBC 8.78 × 10⁹ g/L, PLT 152 × 10⁹ g/L. Coagulation function: APTT 28.0 s, PT 16.3 s, TT 14.5 s, FIB 3.60 g/L, INR 1.51, d-Dimer 1529 ng/mL. Blood ammonia 44.8 umol/L. Biochemical results: ALT 40.6 U/L, AST 75.1 U/L, TP 58.2 g/L, ALB 30.7 g/L, TBIL 297.2 umol/L, DBIL 272.8 umol/L, GGT 276 U/L, UREA 10.6 umol/L, CRE 84 umol/L. Abdominal CT showed cirrhosis and ascites, hepatic portal space occupying, expansion of intrahepatic and extrahepatic bile ducts, portal vein thickened and filling defect which was suspected emboli. The patient was treated with symptomatic and supportive treatment. Three days later, the patient’s heart rate and blood pressure could not be maintained and he died.

23.4.3 Review and Treatment

23.4.3.1 Pathogeny

The etiology of liver failure includes hepatitis virus, drugs, hepatotoxic substances, acute fatty liver disease of pregnancy, pathogen infection, and autoimmune liver disease. In China, HBV infection is the main cause of liver failure, followed by drug and alcohol abuse. In Europe and the United States, alcohol abuse and drugs are the main causes of liver failure, especially caused by acetaminophen which accounts for 40%. The most common cause of liver failure in children is genetic and metabolic diseases. The precipitating factors of liver failure include HBV reactivation, overlapping infection of other hepatotropic or nonhepatotropic virus, bacterial infection, gastrointestinal bleeding, virus mutation, and nonstandard antiviral treatment [65–68] (Table 23.2).
Pathogenesis and Lethal Mechanism

Pathogenesis
The etiology and pathogenesis of liver failure are various and complicated which involve many factors. Hepatocyte mass necrosis, inflammatory cell infiltration, and hepatic ischemic necrosis are the key problems. The main factors involved in the development of liver failure include direct damage of virus or drug, related immune response, and injury caused by precipitating factors. Cellular immunity which involved mainly CTL plays a key role in clearing cytotoxin and is also the main factor causing cell apoptosis or death. In the innate immune cells, macrophages and Kupffer cells proliferate and secrete a large number of cytokines, which induce cytokine storm and delayed hypersensitivity and mediate apoptosis or death of liver cells through death receptors. In addition, the retention and accumulation of endotoxin and metabolites can lead to liver cell injury and rapid deterioration [69].

Systemic Inflammatory Response Syndrome and Multiple Organ Failure
In liver failure, various pathogenic factors not only directly damage liver cells, but also activate inflammatory cells such as monocytes and macrophages, releasing a large amount of inflammatory mediators (TNF-α, interleukin-10, interferon inducible protein 10, vitamin D receptor, human leukocyte antigen, NO, etc.) or
cytokines, which in turn activate monocytes and macrophages to form “cytokine burst.” A large number of cytokines, small-molecular weight toxins, and vasoactive substances cause a sharp increase in inflammatory mediators, forming a network system of inflammatory mediators, which eventually leads to immune dysfunction, uncontrolled body inflammatory response, and multiple organ failure [70].

DIC
The pathogenesis of DIC in liver failure is mainly endotoxin theory. In liver failure, the reticuloendothelial system is not functional enough to remove various substances. Endotoxin can directly activate FXII, damage capillary endothelial cells, and activate the coagulation system. Viruses, antigen-antibody complexes, drugs, and a large amount of tissue thromboplastin-like substances released by hepatocyte necrosis can cause coagulation system activation, platelet activation, fibrin deposition, resulting in diffuse microthrombosis in microvessels, and coagulation factor and platelet reduction by consumption, which is accompanied by secondary hyperfibrinolysis and prompt DIC. DIC itself and shock, multiple organ failure which caused by DIC can lead to sudden death [70].

Classification, Staging, and Diagnosis of Liver Failure
The classification and stages of liver failure are not uniform at present. Based on the medical history, onset characteristics, disease progression speed, and histopathological characteristics of liver failure, China’s 2018 guidelines for the diagnosis and treatment of liver failure classified liver failure into four categories [65]: acute liver failure (ALF), subacute liver failure (SALF), acute-on-chronic (subacute) liver failure (ACLF or SACLF), and chronic liver failure (CLF). (1) Acute liver failure: acute onset, complicated with grade II or higher hepatic encephalopathy, within 2 weeks without underline liver disease; the histology includes necrosis that can be massive, submassive, or bridging, accompanied by severe degeneration of surviving liver cells, and with no collapse or no complete collapse in the hepatic sinus network scaffold. (2) Subacute liver failure: the onset of the disease is slower than ALF. The clinical manifestations occur within 2–26 weeks. The pathological features mainly include co-existence of previous and new submassive necrosis or bridging necrosis. Collapsed reticular fiber or collagen fiber deposition may exist in older necrotic areas; residual hepatocytes have varying degrees of regeneration; and small bile duct hyperplasia and cholestasis can be seen. (3) Acute-on-chronic (subacute) liver failure: acute or subacute deterioration of liver function without chronic liver diseases. The pathological features are as follows: new hepatocyte necrosis can be seen in the background of pathological damage caused by chronic liver diseases. (4) Chronic liver failure: in patients with liver cirrhosis, progressive deterioration and liver decompensation developed, accompanied with ascites and/or hepatic encephalopathy. The histology includes diffuse hepatic fibrosis and the formation of dysplastic nodules with unevenly distributed hepatocyte necrosis. The staging and diagnosis of each type of liver failure are shown in Table 23.3 [71].
### 23.4.3.3 Treatment

Principles of treatment include early detection, diagnosis, and treatment. Comprehensive medical treatment should be based on the etiology. Active prevention and treatment of complications, artificial liver, and liver transplantation are also very important.

#### General Symptomatic Supportive Treatment

(1) The removal of precipitating factors: identify overlap infection with other hepatotrophic or nonhepatotrophic virus and bacteria, gastrointestinal bleeding, various stress states, fatigue, alcohol consumption, incorrect treatment, etc. (2) Reduce liver burden: bed rest, reduce physical exertion, strengthen the supply of nutrition and energy, and avoid the application of drugs causing liver injury. (3) Improve the liver function: by inhibiting liver inflammation, removing reactive oxygen species, promoting biological transformation and detoxification, stabilizing the cell membrane, improving cell membrane fluidity and integrity, regulating energy metabolism, reducing liver tissue damage, promoting liver cell repair and regeneration, and

---

**Table 23.3** Classification and diagnosis of liver failure

| Classification                  | Diagnosis                                                                 |
|---------------------------------|---------------------------------------------------------------------------|
| Acute hepatic failure           | Acute onset, complicated with grade II or higher hepatic encephalopathy, within 2 weeks without underlying liver disease and has the following behavior: (1) extreme fatigue, accompanied by obvious anorexia, abdominal distension, nausea, vomiting, and severe gastrointestinal symptoms; (2) jaundice gradually deepened in a short period, and serum total bilirubin (TBil) ≥ 10× upper limit of normal value (ULN) or daily increase ≥17.1 mol/L; (3) bleeding tendency, prethrombin activity (PTA) ≤ 40%, or international standardized ratio (INR) ≥ 1.5, and other reasons were excluded; (4) progressive shrinkage of the liver |
| Subacute liver failure          | The onset of the disease is slower than ALF and the following manifestations at 2–26 weeks: (1) extreme weakness and obvious gastrointestinal symptoms; (2) jaundice rapidly deepened, serum Tbil ≥10× ULN or daily increase ≥17.1 mol/L; (3) with or without hepatic encephalopathy; (4) those with bleeding, PTA ≤ 40% (or INR ≥ 1.5) and other reasons excluded |
| Acute-on-chronic (subacute) liver failure | Hepatorenal syndrome, hepatopulmonary syndrome and other complications, as well as extrahepatic organ failure in patients with chronic liver diseases. Patients with jaundice rapidly deepened, serum Tbil ≥10× ULN or daily increase ≥17.1 mol/L; there was bleeding, PTA ≤ 40% (or INR ≥ 1.5). On the basis of different chronic liver diseases, it can be divided into three types. Type A: chronic noncirrhotic liver diseases with slow and acute liver failure; Type B: chronic plus acute liver failure on the basis of compensatory cirrhosis, usually within 4 weeks; and Type C: chronic plus acute liver failure on the basis of decompensated cirrhosis |
| Chronic liver failure           | In patients with liver cirrhosis, progressive deterioration and liver decomposition developed: (1) serum TBil increased, often <10 × ULN; (2) albumin (Alb) decreased significantly; (3) platelets decreased significantly, PTA ≤ 40% (or INR ≥1.5), and other reasons were excluded; (4) refractory ascites or portal hypertension; (5) hepatic encephalopathy |
reducing intrahepatic cholestasis, so as to improve the liver function. Anti-inflammatory drugs (glycyrrhizin), liver membrane protectants, antidotes, and anti-cholinergic drugs are recommended. (4) Nutritional support: recommend enteral nutrition, including high-carbohydrate, low-fat, and moderate protein diet. Intravenous supplement of calories, fluids, vitamins, and trace elements are recommended in patients with poor food intake. Also, night snack is recommended. (5) To correct hypoproteinemia and maintain water and electrolyte balance, especially to correct low sodium, low chlorine, low magnesium, low potassium; supplement coagulation factors and improve liver circulation. (6) Closely detect the change of illness and strengthen nursing management [65].

Etiological Treatment

*Hepatitis virus infection*: Mainly targeted at liver failure patients affected by HBV and HCV infection. For HBVDNA-positive patients, early and rapid reduction of HBVDNA load is the key to treatment. It is recommended to use nucleoside (acid) drugs for antiviral treatment immediately. Fast and effective nucleoside (acid) drugs are recommended, such as entecavir and tenofovir. Direct-acting antiviral agents are preferred in patients who are HCV RNA positive. Individualized treatment is carried out according to HCV genotype and patient tolerance, but the protease inhibitor is contraindicated in decompensated cirrhosis, which can aggravate the progress of liver failure. In the clinic, there is no special and effective treatment for end-stage liver failure caused by HCV infection. Liver transplantation may be the best treatment. For patients with confirmed or suspected herpes virus or varicella-zoster virus infection resulting in acute liver failure should be treated with acyclovir (5–10 mg/kg, 1 time /8 h, intravenous drip) [65].

*Liver failure caused by drug-induced liver injury*: Stopping all suspicious drugs on time. For patients with acute liver failure caused by excessive acetaminophen (APAP), if the intake of APAP happens within 4 h, the active peptide should be taken orally before the administration of N-acetylcysteine (NAC). For patients with large intake of APAP, the elevation of the serum drug concentration or transaminase indicates that liver injury is imminent or has occurred. NAC should be given immediately and artificial liver therapy should be carried out if necessary. NAC can improve the prognosis of mild hepatic encephalopathy in patients with acute liver failure caused by nonAPAP, and should be applied as early as possible. Penicillin G and silymarin should be considered for patients with acute liver failure diagnosed or suspected of mushroom poisoning [72].

*Alcoholic liver failure*: Abstinence is the basis of treatment. Patients with severe alcoholic liver disease with Maddary score ≥ 32 can be treated with corticosteroid, usually at a dose of prednisone of 40 mg/day for 1 month. Infection should be closely monitored before and during treatment. The response to hormone can be evaluated by Lille score when corticosteroid is used for 7 days. If the Lille score ≥ 0.56 on day 7 after treatment, corticosteroid should be stopped in time. N-acetylcysteine can be used in combination with corticosteroid. Some studies have reported that combined treatment can reduce the occurrence of severe alcoholic liver disease infection and hepatorenal syndrome [73, 74].

*Autoimmune liver disease*: For liver failure caused by autoimmune hepatitis, early use of corticosteroid (methylprednisolone, 1.0–1.5 mg/kg/day) may be
effective, and liver transplantation should be considered if the treatment fails for a week [75].

**Acute fatty liver/HELLP syndrome in pregnancy:** Termination of pregnancy immediately. If the disease continues to progress after termination of pregnancy, artificial liver and liver transplantation should be considered [65].

**Hepatolenticular degeneration:** It can be treated with penicillamine and other copper expelling drugs, but the general curative effect is not good for liver failure patients. Plasma exchange, albumin dialysis, hemofiltration, and artificial liver support therapy combined with various blood purification methods can be used. Liver transplantation should be considered as early as possible for patients with end-stage liver failure [76].

### 23.4.3.4 Prevention and Treatment of Complications

**Brain edema:** Intracranial pressure should be reduced in time in patients with intracranial hypertension. Mannitol (0.5–1.0 g/kg) or hypertonic saline should be used as soon as possible, and alternately using loop diuretics such as furosemide and osmotic dehydrating agents, and supplement human blood albumin which can improve colloid osmotic pressure and relieve brain edema. Also, artificial liver support therapy can be used. Mild hypothermia therapy can be considered for acute liver failure patients with uncontrollable intracranial hypertension, and indomethacin can be given to control intracranial hypertension under the condition of high cerebral blood perfusion.

**Hepatic encephalopathy:** Remove the predisposing factors using lactulose and ornithine-aspartic acid to reduce blood ammonia. Timely find infection and give anti-infection treatment to reduce systemic inflammatory response.

**Infection:** Prophylactic use of anti-infection drugs is not recommended. Attention should be paid to monitoring. The most common sites of infection are abdominal cavity, lungs, urinary tract, and blood. Once infection is found, antibiotics should be used empirically and immediately, and adjusted in time according to culture results.

**Hyponatremia:** Dilute hyponatremia caused by water and sodium retention is most common. When blood sodium is lower than 125 mmol/L, water can be properly limited. Hypertonic saline can quickly correct hyponatremia, but it will cause more water and sodium retention. Therefore, hypertonic saline solution is generally not recommended to correct hyponatremia. If there is severe hyponatremia (blood sodium level <110 mmol/L) or hyponatremia encephalopathy occurs, 50–100 mL of 3–5% NaCl solution can be appropriately added intravenously. Tolvaptan, an arginine vasopressin V2 receptor blocker, mainly promotes free water excretion and corrects hyponatremia by selectively blocking the V2 receptor of collecting duct main cells. During application, the urine volume, physical signs, and electrolyte of patients should be closely monitored, and the increasing rate of blood sodium within 24 h should not exceed 12 mmol/L.

**Refractory ascites:** Low salt diet, 4–6 g/day. Furosemide combined with spironolactone can be used. Tolvaptan can be used in patients with poor response. Vasoactive drugs, such as midodrine and terlipressin, can improve the patient’s hyperdynamic circulatory state to a certain extent and increase the body’s response to diuretics. Patients with severe ascites may undergo paracentesis to release ascites, which can quickly relieve abdominal distension symptoms. However, we should be alert to...
circulatory dysfunction after releasing ascites, and it can be prevented by giving albumin infusion or vasoactive drugs.

**Acute renal injury (AKI):** AKI is one of the common complications of liver failure. Once AKI occurs, the prognosis is poor. Prerenal AKI is the most common form. Hepatorenal syndrome (HRS) is a special form of prerenal AKI. Once AKI occurs in patients with liver failure, possible renal injury drugs, vasodilators or non-steroidal anti-inflammatory drugs, should be discontinued. Use albumin or crystal solution to expand the volume. If infection is suspected, the infection should be controlled as soon as possible. If AKI does not improve after volume expansion, HRS should be considered and vasoconstrictors (terlipressin or norepinephrine) combined with albumin can be used for treatment. If terlipressin (1 mg/4–6 h) combined with albumin (20–40 g/day) is applied, the serum creatinine decreases by <25% after 3 days, and terlipressin can be gradually increased to 2 mg/4 h. If effective, the course of treatment is for 7–14 days; If not, stop using terlipressin. Norepinephrine (0.5–3.0 mg/h) combined with albumin (10–20 g/L) is also effective on HRS, but its effect is currently reported to be not as good as that of terlipressin. AKI, which is ineffective with vasoconstrictive drugs and meets the criteria of renal replacement therapy, can be treated with renal replacement therapy.

**Artificial liver:** Its therapeutic mechanism is based on the strong regeneration ability of liver cells. Through an external mechanical, physical, chemical, and biological device, it removes various harmful substances, supplements necessary substances, improves internal environment, and temporarily replaces some functions of failing liver, to create conditions for liver cell regeneration and liver function recovery or to wait for an opportunity for liver transplantation. Artificial liver support system can be divided into three types: nonbiological, biological, and combined system. Nonbiological artificial liver has been widely used in the clinic and proved to have certain effect.

**Liver transplantation:** Liver transplantation is the best choice for patients who have failed to respond to aggressive medical treatment. The MELD score is the main reference for evaluating liver transplantation [77].

### 23.4.4 Discussion

In the above cases, the patient is a middle-aged male with a long history of alcohol consumption and lack of health awareness, and the liver tumor was found to be terminal. And one of the hallmarks of a liver tumor in its end stages is liver failure. In the course of liver tumor development, necrosis and abnormal liver cells inevitably occur until the normal liver function is completely lost. As a secondary change of advanced liver tumor, liver failure plays an important role in predicting prognosis. On the basis of clear treatment of primary disease, targeted treatment is an effective method to treat liver failure. Another problem is the economics of treating liver failure. Despite the availability of advanced treatments like artificial livers and liver transplants, recipients are small, and few families can afford such high costs without health insurance.
23.4.5 Conclusion

By sharing the death case of liver failure, we aim to understand the course of death from sudden death caused by liver failure and to find better treatments to save more patients. Although there are so many treatments available to intervene in liver failure, a large number of patients with liver failure still die each year without timely and effective treatment. So, we still have a long way to go.

23.5 Acute Suppurative Cholangitis

23.5.1 Introduction

Acute suppurative cholangitis refers to various causes of biliary stenosis, secondary cholestasis, and acute suppurative bile duct infection. In physiological condition, continuous bile secretion and immune barrier of the bile duct epithelium can keep the bile duct sterile. The benign and malignant causes (stones, tumors, etc.) of the bile duct lead to biliary stricture or obstruction, which elevates the pressure within the biliary system, destroys the normal immune barrier, flushes the bacteria and endotoxins from the infected bile into systemic circulation, and induces systemic inflammatory response syndrome. The mortality of acute suppurative cholangitis can reach as high as 50%, if biliary decompression and drainage are not provided immediately [78, 79]. Here we will discuss the mechanisms of death caused by acute suppurative cholangitis and the diagnosis and treatment strategy based on a clinical case.

23.5.2 Case and Method

The case occurred in October 2019. We analyzed the death process by reviewing the clinical symptoms, examination results, test results, and clinical treatment of the patient. The case sharing has been approved by the ethics committee of our hospital.

23.5.2.1 Case Report

An 89-year-old male patient was admitted to our hospital complaining of “jaundice for 14 days, and fever accompanied by asthma for 5 days.” Past history includes hypertension and coronary artery stent implantation. Vital signs: T 36.7 °C, P 82/min, R 31/min, BP 160/79 mmHg, SPO2 94%. Physical examination revealed jaundice and tenderness of the right upper abdomen, rebound pain, and muscle tension. Laboratory tests: Hb 95 g/L, HCT 0.252 L/L, WBC 19.01 × 10^9 g/L, PLT 102 × 10^9 g/L, APTT 28.6S, PT 12.8S, TT 13.0S, FIB 3.93 g/L, INR 1.19, d-dimer 2028 ng/mL, ALT 213.3 U/L, AST 126.2 U/L, TP 60.3 g/L, ALB 32.5 g/L, TBIL 158.2 umol/L, DBIL 132.6 umol/L, GGT 675 U/L, CRP 80 mg/dL, PCT 21.25 ng/mL. Abdominal ultrasound showed extrahepatic bile duct expansion and gallbladder wall thickening. The patient received anti-infection, rehydration, and other conservative treatment. The patient could not tolerate the invasive procedure of ERCP because of his old age, and finally died after 2 days of hospitalization.
23.5.3 Review and Management

23.5.3.1 Etiology and Incentives
The occurrence of acute suppurative cholangitis mainly depends on two factors: biliary obstruction and bacterial growth in the bile duct. A variety of causes can lead to bile duct stenosis or obstruction, and then induce acute suppurative cholangitis. Cholelithiasis is the most common cause of benign biliary obstruction and cholangitis, accounting for about half of the cases of acute suppurative cholangitis [80]. Other causes of benign biliary obstruction include benign stricture, external compression, and autoimmune diseases. The causes of malignant biliary obstruction include cholangiocarcinoma, gallbladder cancer, pancreatic cancer, ampullary cancer, and duodenal cancer. Secondary malignant obstruction of the biliary tract accounts for 10–30% of acute suppurative cholangitis [81].

The main route for bacteria to enter the bile duct is through retrograde infection from the duodenum. In addition, the bile duct can also be infected through the portal vein system and the periportal lymphatic system [82]. The most common pathogens of acute suppurative cholangitis include *Escherichia coli*, *Klebsiella*, and *Enterococcus* [83]. However, anaerobes and a variety of microorganisms are often found in patients with a previous history of biliary tract operation, in patients with severe concomitant diseases, and the elderly [84].

23.5.3.2 Lethal Mechanism
*Septic shock*: In acute suppurative cholangitis, the increased pressure within the bile duct disrupts the tight junctions between the epithelial cells of the bile duct, and flushes a large number of microorganisms and endotoxins from the infected bile into systemic circulation, leading to a systemic inflammatory cascade reaction and septic shock, which is one of the main causes of death in patients with acute suppurative cholangitis [85].

*Multiple organ dysfunction syndrome (MODS)*: MODS is another important cause of death in patients with acute suppurative cholangitis. Bacteremia and endotoxemia lead to the activation of inflammatory cells in the body, excessive release of many kinds of inflammatory cytokines such as tumor necrosis factor and interleukin-6 into the circulatory system, resulting in systemic inflammatory cascade reaction, and eventually lead to the occurrence of MODS. Multivariate analysis showed that bacterial infection producing extended spectrum β-lactamases, leukocyte >20,000 cells/μL, serum total bilirubin >10 mg/dL, and an elevated serum urea nitrogen level were the risk factors for MODS, while timely decompression and drainage of the biliary tract were protective factors [86, 87].

23.5.3.3 Diagnosis
In the past, the diagnosis of acute suppurative cholangitis mainly depended on the clinical symptoms of patients. Typical patients may have fever, right upper abdominal pain and jaundice, namely, Charcot’s triad, while severe patients may have shock and neurologic symptoms, namely, Reynolds pentad. However, the sensitivity of these two diagnostic criteria in the diagnosis of acute suppurative
cholangitis is low and therefore not applicable. Initially published in 2007, the Tokyo guidelines established a more comprehensive diagnostic standard based on the clinical signs and symptoms, laboratory examination, and diagnostic imaging of patients. After two evaluations and revisions in 2013 and 2018, it has become a commonly used clinical diagnostic criterion for acute cholangitis (Table 23.4) [88].

**Clinical Signs and Symptoms**
Fever, right upper abdominal pain, and jaundice (Charcot’s triad) are common clinical manifestations of acute suppurative cholangitis, which can be seen in 60–80% of patients. Although the specificity of Charcot’s triad can reach as high as 95.9%, studies have reported its sensitivity to be only 21.2–26.4%. In the same way, Reynolds pentad was only found in 4–8% of the severe patients. Therefore, the clinical application of the diagnostic criteria which only depend on clinical symptoms is seriously limited. In 2007, the Tokyo guideline diagnostic criteria, based on the clinical manifestations, laboratory examination, and diagnostic imaging of patients, were updated in 2013, and the sensitivity for the diagnosis of acute suppurative cholangitis was 91.8%, while the specificity reached 77.7% [88, 89]. Therefore, the 2013 diagnostic criteria for acute cholangitis were adopted by Tokyo Guidelines 2018 and used as the standard criteria in the clinical setting.

**Laboratory Examination**
Inflammatory reaction, cholestasis, and etiological evidence can be found in laboratory examination. Abnormal white blood cell counts (leukocyte (X1000/UL) < 4 or >10), increase of serum creatinine protein levels (C-reactive protein ≥1 mg/dL), and other changes indicate systemic inflammatory response. In addition, procalcitonin (PCT) has been considered as a sensitive indicator of severe bacterial infection and sepsis in recent years, which can be significantly increased in acute suppurative cholangitis. It can be used to assist in assessing the severity of the disease and

| **Table 23.4** Tokyo Guidelines 2018: diagnostic criteria for acute cholangitis |
|---------------------------------------------------------------|
| **A** Systemic inflammation                                     |
| A-1. Fever >38 °C and/or shaking chills                      |
| A-2. Laboratory data: evidence of inflammatory response:WBC(X1000/UL) < 4 or >10, CRP(mg/dL) ≥ 1 |
| **B** Cholestasis.                                             |
| B-1. Jaundice:T-Bil ≥ 2 (mg/dL)                              |
| B-2. Laboratory data: abnormal liver function tests:ALP, GGT, AST, ALT >1.5× STD |
| **C** Imaging.                                                 |
| C-1. Biliary dilatation                                      |
| C-2. Evidence of the etiology on imaging (stricture, stone, stent etc.) |
| Suspected diagnosis: one item in A + one item in either B or C |
| Definite diagnosis: one item in A, one item in B, and one item in C |

| **ALP** alkaline phosphatase, **ALT** alanine aminotransferase, **AST** aspartate aminotransferase, **CRP** C-reactive protein, **GGT** r-glutamyltransferase, **WBC** white blood cell, and **STD** upper limit of normal value |
whether emergency biliary decompression and drainage is needed [90, 91]. Elevated T-Bil, (≥2 mg/dL) ALP, GGT, AST, and ALT levels (>1.5 times the upper limit of normal) are the manifestations of cholestasis. Among them, an increase of ALP can be seen in 74–93% of patients with acute suppurative cholangitis, and ALP recovers faster than other laboratory tests (such as bilirubin) after biliary decompression and drainage. Hence, it can be used as an indicator for judging whether biliary drainage is sufficient [92]. Blood specimen should be sent for culture to identify the causative organisms of acute suppurative cholangitis, and to guide anti-infection treatment. However, positive rates of blood culture range from 21% to 71% for acute suppurative cholangitis, and the procedure is time-consuming, which highly limits its clinical application. Therefore, the Tokyo Guidelines and the American Society of surgical infection/infectious diseases guidelines do not recommend routine blood culture examination [93, 94]. Blood culture was recommended only in a small number of patients with immune deficiency or severe infection, when such results may be helpful to guide the selection and course of antibiotics.

**Imaging Examination**

Imaging examination includes abdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), ERCP, and EUS. Based on the findings of these imaging examinations, we can identify the causes of biliary stenosis/blockage that can cause acute cholangitis (stenosis, stone, stent, etc.). Abdominal ultrasound is often used as the first choice because of its minimal invasiveness, wide availability, convenience, and low price. It can detect abnormal dilatation of the bile duct and identify its causes. However, due to the influence of factors such as intestinal gas accumulation, it is easy to miss the diagnosis of distal choledocholithiasis and malignant lesions of the bile duct. Thus, abdominal ultrasound has a low diagnostic sensitivity. A meta-analysis showed that abdominal ultrasound has a sensitivity of 42% (95% CI: 28 to 56%) and a specificity of 96% (95% CI: 94 to 98%) for dilated common bile duct and a sensitivity of 38% (95% CI: 27 to 49%) and a specificity of 100% (95% CI: 99 to 100%) for all bile duct stones. Abdominal enhanced CT can be used to identify the causes of biliary obstruction such as cholelithiasis, benign strictures, and malignancies [95]. However, due to the presence of X-ray negative stones, it has a low sensitivity of 42% for bile duct stones [96]. MRCP can clearly delineate the morphology of intrahepatic and extrahepatic bile duct and pancreatic duct without the use of a contrast agent, and identify bile duct stenosis, dilatation, and large stones in the common bile duct. However, MRCP has a low diagnostic accuracy when displaying stones less than 6 mm [97]. ERCP is an invasive diagnostic and therapeutic procedure. It is the gold standard for the diagnosis of acute suppurative cholangitis, when the pus overflow was seen at the duodenal papilla through a duodenoscope. ERCP cholangiography can also show the delineation of the whole biliary tree, and find the cause of cholangitis. With the wide accessibility of MRCP, ERCP is now rarely used only for diagnostic purpose. ERCP has been recommended as the first-line biliary drainage procedure for acute cholangitis because of its less invasiveness and lower risk of adverse events than other drainage techniques [98]. In recent years, EUS has been emerging as a novel technique which provides both diagnostic and therapeutic effects for acute cholangitis. It demonstrates a sensitivity of nearly 100% and a
specificity of more than 90% to the diagnosis of cholelithiasis, which is significantly better than MRCP, especially for the detection of small stones that are not easy to be identified by other inspection measures. EUS is superior to ERCP in the detection of cholangiopancreatic tumors, tumor invasion, and lymph node metastasis. In addition, EUS guided biliary drainage has been developed and reported as a useful alternative drainage technique when ERCP intubation fails [99, 100].

**Severity Grading Criteria for Acute Cholangitis**

Based on patients’ clinical signs and symptoms and routine laboratory examinations and whether or not combined with organ dysfunction, acute cholangitis was divided into three grades: mild, moderate, and severe (grade I, II, III) in Tokyo Guidelines of 2013. This severity grading criteria can be used to predict the prognosis of patients with acute cholangitis and determine which patients need emergency biliary decompression and drainage. Four case series studies from Japan and Taiwan confirmed its prognostic value in clinical application, and two of them evaluated the severity grading criteria as an indicator for biliary drainage. In these studies, patients with a higher severity grading had significantly higher 30-day mortality. However, 30-day mortality was significantly lower in patients with Grade II acute cholangitis who were treated with early or urgent biliary drainage. These findings suggest that the severity grading criteria in the Tokyo Guidelines of 2013 can be used to identify Grade II patients whose prognoses may be improved through urgent biliary drainage. Thus, this severity grading criteria were adopted in the Tokyo Guidelines of 2018 and used as the standard in the clinical setting (Table 23.5) [88].

**Table 23.5** Severity grading criteria for acute cholangitis in the Tokyo Guidelines of 2018

| Grade III (severe) acute cholangitis |
|-----------------------------------|
| “Grade III” acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction at least in any one of the following organs/systems: |
| 1. Cardiovascular dysfunction: hypotension requiring dopamine $\geq 5 \mu g/kg/min$, or any dose of norepinephrine |
| 2. Neurological dysfunction: disturbance of consciousness |
| 3. Respiratory dysfunction: $P_{a}O_{2}/F_{i}O_{2}$ ratio $< 300$ |
| 4. Renal dysfunction: oliguria, serum creatinine $>2.0 \text{ mg/dL}$ |
| 5. Hepatic dysfunction: PT-INR $> 1.5$ |
| 6. Hematological dysfunction: platelet count $< 100,000/\text{mm}^3$ |

| Grade II (moderate) acute cholangitis |
|-------------------------------------|
| “Grade II” acute cholangitis is associated with any two of the following conditions: |
| 1. Abnormal WBC count ($>12,000/\text{mm}^3$, $<4000/\text{mm}^3$) |
| 2. High fever ($\geq 39 \text{ °C}$) |
| 3. Age ($\geq 75 \text{ years old}$) |
| 4. Hyperbilirubinemia (total bilirubin $\geq 5 \text{ mg/dL}$) |
| 5. Hypoalbuminemia ($< \text{STD} \times 0.7$) |

| Grade I (mild) acute cholangitis |
|---------------------------------|
| “Grade I” acute cholangitis does not meet the criteria of “Grade III (severe)” or “Grade II (moderate)” acute cholangitis at initial diagnosis. |

*STD: lower limit of normal value*
23.5.3.4 Management

Initial Management
Initial medical treatment includes the infusion of sufficient fluids and electrolytes, as well as analgesic administration and other symptomatic treatment. Empirical anti-infection therapy should be started as soon as a definitive diagnosis of acute cholangitis has been reached. Severity should be assessed according to the severity grading criteria for acute cholangitis. Moderate and severe patients should be fasting to enable immediate emergency drainage. At the same time, vital signs including blood pressure, heart rate, respiration rate, temperature, urine volume, oxygen saturation (SPO2), and the patient’s general status should be evaluated and closely monitored.

Management Based on the Severity Grading of Acute Cholangitis
Acute cholangitis should be managed in accordance with its severity. Alongside the initial treatment, severity assessment should be carried out using the severity grading criteria for acute cholecystitis in the Tokyo Guidelines of 2018. Timing treatment should be provided for patients based on the severity grading of acute cholangitis (Fig. 23.1) [100]. And the patient’s general status and severity of disease should be reassessed within 24 h, 24–48 h after the start of treatment.

Grade I (mild acute cholangitis): After initial treatment including antibiotics and general supportive care, most of the patients with mild acute cholangitis will get better without biliary drainage. However, if the patient’s condition does not improve within 24 h after initial treatment, biliary drainage should be considered. For patients with choledocholithiasis, choledocholithotomy may be performed at the same time as biliary drainage.

Grade II (moderate acute cholangitis): In addition to the initial treatment including antibiotics and general supportive care, patients with moderate acute cholangitis should consider early biliary drainage, including ERCP, PTBD, and EUS-BD. Treatment for the underlying etiology (bile duct stones, tumor, etc.) should

![Flowchart for the management of acute cholangitis in the Tokyo Guidelines of 2018](image-url)
not be provided until the patient’s general condition has improved after early biliary drainage.

**Grade III (severe acute cholangitis):** Severe acute cholangitis is characterized by sepsis-induced organ dysfunction. The condition of patients with severe cholangitis may deteriorate rapidly. In addition to the initial treatment, organ function support should be given immediately, including noninvasive/invasive mechanical ventilation (tracheal intubation followed by artificial ventilation) and vasoactive drugs. Urgent biliary drainage, including ERCP, PTBD, and EUS-BD, should be performed immediately after the patient’s vital signs are stable. If the hospital is unable to perform such operations, the patient should be transferred to a hospital that can perform biliary drainage. The treatment of biliary obstruction should be delayed until the patient’s condition is stable.

**Antimicrobial Recommendations for Acute Cholangitis**

The primary goal of antimicrobial treatment for patients with acute suppurative cholangitis is to control sepsis and local inflammation of the bile duct and prevent the formation of intrahepatic abscess. Therefore, once suspected of acute suppurative cholangitis, empirical antimicrobial treatment should be provided immediately.

The common pathogens of acute suppurative cholangitis include *Escherichia coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, *Acinetobacter*, etc. The selection of empiric antibiotics mainly depends on the type of strains prevalent in the area and the data of antimicrobial susceptibility. Common antibiotics include penicillins, cephalosporins, carbapenems, fluoroquinolones, etc. The resistance of *Enterobacteriaceae* strains has been widely reported, especially the gram-negative bacilli producing β-lactamase (ESBL) and carbapenemase, which have significantly affected the empirical antibacterial treatment of acute cholangitis. The Tokyo Guidelines of 2018 recommended that bile samples should be taken for bacterial culture and antimicrobial susceptibility test during biliary drainage. Once causative microorganisms and the susceptibility testing results are available, the application of antimicrobial therapy should be adjusted to specific antimicrobial agents targeting the organisms [94]. The guideline also recommends drug selection of empirical antibacterial treatment for community-acquired biliary tract infection and iatrogenic biliary tract infection; see Table 23.6 for details [94].

**Choice of Biliary Drainage**

Patients with moderate or severe acute cholangitis should be treated with early/urgent biliary drainage. Drainage methods include endoscopic transpapillary drainage, percutaneous transhepatic drainage, and surgical drainage.

**ERCP**

ERCP has become the first-line of therapy for acute cholangitis because of its less invasiveness and lower risk of adverse events compared to other drainage techniques. Endoscopic transpapillary biliary drainage methods include external drainage via nasobiliary catheters and internal drainage via biliary stents. Both methods were equally effective for patients with acute suppurative cholangitis. There is no significant difference in the success rate, effectiveness, and complications between the two procedures. The advantages of nasobiliary catheters over internal stents are the ability to obtain noninvasive cholangiograms and cholecystograms; to monitor
### Table 23.6 Antimicrobial recommendations for acute cholangitis in the Tokyo Guidelines of 2018

| Severity | Community-acquired biliary infections | Grade I | Grade II | Grade III<sup>a</sup> | Healthcare-associated biliary infections<sup>a</sup> |
|----------|---------------------------------------|---------|----------|-----------------------|-----------------------------------------------|
|          |                                       |         |          |                       |                                               |
| Antimicrobial agents | Cholangitis and cholecystitis | Cholangitis and cholecystitis | Cholangitis and cholecystitis | Healthcare-associated cholangitis and cholecystitis |
| Penicillin-based therapy | Ampicillin/sulbactam<sup>b</sup> is not recommended if >20% resistance rate. | Piperacillin/tazobactam | Piperacillin/tazobactam | Piperacillin/tazobactam |
| Cephalosporin-based therapy | Cefazolin,<sup>c</sup> or Cefotiam,<sup>c</sup> or Cefuroxime,<sup>c</sup> or Ceftriaxone,<sup>c</sup> or Ceftriaxone ± Metronidazole<sup>d</sup> Cefmetazole,<sup>c</sup> Cefoxitin<sup>c</sup> Flomoxef<sup>c</sup> Cefoperazone/sulbactam | Ceftriaxone, or Cefotaxime, or Cefepime, or Cefozopran, or Ceftazidime ± Metronidazole<sup>d</sup> Cefoperazone/sulbactam | Cefepime, or Ceftazidime, or Cefozopran ± Metronidazole<sup>d</sup> Cefoperazone/sulbactam | Cefepime, or Ceftazidime, or Cefozopran ± Metronidazole<sup>d</sup> |
| Carbenem-based therapy | Ertapenem | Ertapenem | Imipenem/cilastatin, meropenem, doripenem, ertapenem | Imipenem/cilastatin, meropenem, doripenem, ertapenem |
| Monobactam-based therapy | – | – | Aztreonam ± metronidazole<sup>d</sup> | Aztreonam ± metronidazole<sup>d</sup> |
| Fluoroquinolone-based therapy<sup>e</sup> | Ciprofloxacin, Levofloxacin, Pauflxacin ± Metronidazole<sup>d</sup> Moxifloxacin | Ciprofloxacin, Levofloxacin, Pauflxacin ± Metronidazole<sup>d</sup> Moxifloxacin | Ciprofloxacin, Levofloxacin, Pauflxacin ± Metronidazole<sup>d</sup> Moxifloxacin |

<sup>a</sup>Vancomycin is recommended to cover Enterococcus spp. for grade III community-acquired acute cholangitis and cholecystitis, and healthcare-associated acute biliary infections. Linezolid or daptomycin is recommended if vancomycin-resistant Enterococcus (VRE) is known to be colonizing the patient, if previous treatment included vancomycin, and/or if the organism is common in the community.

<sup>b</sup>Ampicillin/sulbactam has little activity left against Escherichia coli. It is removed from the North American guidelines.

<sup>c</sup>Local antimicrobial susceptibility patterns (antibiogram) should be considered for use.

<sup>d</sup>Anti-anaerobic therapy, including use of metronidazole, tinidazole, or clindamycin, is warranted if a biliary-enteric anastomosis is present. The carbapenems, piperacillin/tazobactam, ampicillin/sulbactam, cefmetazole, cefoxitin, flomoxef, and cefoperazone/sulbactam have sufficient anti-anaerobic activity for this situation.

<sup>e</sup>Fluoroquinolones use is recommended if the susceptibility of cultured isolates is known or for patients with b-lactam allergies. Many extended-spectrum b-lactamase (ESBL)-producing Gram-negative isolates are fluoroquinolone resistant.
the drainage volume; and to provide irrigation for hemobilia, mucin, or debris. However, it suffers from the disadvantage of patient discomfort and risk for dislodgement. On the other hand, the internal stents are associated with less postprocedure discomfort and avoid the potential problems of inadvertent removal of the nasobiliary catheter. The major drawbacks of the internal stent are that its patency and adequacy of drainage cannot be monitored. Furthermore, it has been found with a higher rate of blockage and more frequent hyperamylasemia. Thus, the choice of endoscopic transpapillary drainage, nasobiliary catheters, or biliary stents depends on the preference of the operator and the specific circumstances of each patient [101].

EUS-BD
EUS-BD has become the first-line of alternate therapeutic modality for biliary obstruction in patients who fail ERCP. The indications for EUS-BD include failure of ERCP intubation, and cases of benign and malignant bile duct obstruction that cannot be intubated by conventional transpapillary biliary drainage methods. The latter includes anatomical abnormalities after surgery and obstruction of the gastroduodenal lumen. Relative contraindications to EUS-BD are ascites, recent surgery, and anticoagulation therapy. EUS-BD consists of two puncture routes: intrahepatic and extrahepatic. Under the guidance of EUS, the intrahepatic puncture route is from the stomach to the left intrahepatic bile duct, while the extrahepatic puncture route is from the duodenum to the common bile duct. Once the puncture is successful, different drainage methods can be selected according to the etiology and anatomy of the obstruction, mainly including EUS-guided rendezvous technique (EUS-RV), EUS-guided antegrade stenting (EUS-AS), and EUS-guided transmural stenting (EUS-TS), which includes EUS-guided gastrostomy (EUS-HGS) and EUS-guided choledochoduodenostomy (EUS-CDS) according to different puncture sites. Compared with PTBD, EUS-BD has a higher success rate, while the incidence of adverse events is lower. Moreover, EUS-BD provides internal drainage, which is more in line with physiological conditions. Therefore, at present, EUS-BD has basically replaced PTBD as the first alternative measure for patients with acute supplicative cholangitis when ERCP is not an option [102].

PTBD
PTBD is another alternative to biliary drainage in patients with ERCP intubation failure. The technical success rate of PTBD is more than 90% in patients with intrahepatic bile duct dilation. However, the incidence of adverse events can be as high as 40%, including postprocedure bile leak, bleeding, cholangitis, drainage stent blockage or displacement, etc. PTBD is currently mainly used in patients with failed EUS-BD procedures. In addition, PTBD remains an alternative biliary drainage after ERCP failure in hospitals where EUS-BD is unavailable [103].

Surgical Drainage
Open surgical drainage was used to treat biliary obstruction and cholangitis before the introduction of endoscopic drainage and PTBD. At present, surgical drainage is not the first choice for patients with acute cholangitis because of its high incidence
of complications. It is only performed when endoscopic or other drainage procedures have failed, as well as for patients with acute suppurative cholangitis who need surgery because of the primary disease [104].

23.5.4 Discussion

In the above-mentioned case, the patient was an old man with a history of hypertension and coronary heart disease, so the risk of operation was very high. ERCP is the first choice for patients with acute suppurative cholangitis. However, the patient cannot tolerate the ERCP procedure due to his poor physical condition. For elderly patients with acute suppurative cholangitis, the risk of sudden death is very high due to uncorrectable septic shock and continuous deterioration of the liver function.

23.5.5 Conclusion

For patients with acute suppurative cholangitis, the probability of sudden death is very low as long as the diagnosis is timely. After the biliary obstruction was relieved, the infection was more easily controlled and the probability of MODS was greatly reduced. Based on the characteristics of this disease, we need to ensure timely diagnosis.

23.6 Acute Pancreatitis

23.6.1 Introduction

Acute pancreatitis (AP) is defined as an inflammatory response after abnormal trypsinogen activation due to a variety of causes, followed by autodigestion of pancreas [105]. In severe cases, systemic inflammatory response syndrome occurs, and it can be accompanied by other organ dysfunction diseases. The process of most patients is self-limiting. About 15% of patients progress to severe acute pancreatitis with an overall mortality rate of 5–10%. Patients with severe pancreatitis have a higher mortality rate of 34–55% [106, 107]. According to autopsy data statistics, sudden death caused by acute pancreatitis is one of the important causes of noncardiac sudden death, which accounts for 0.2–2.5% of natural sudden death [108]. We understand the dangers of acute pancreatitis through a case report.

23.6.2 Case and Method

This death occurred in August 2019. We analyzed the death process by reviewing the clinical symptoms, laboratory tests, imaging tests, and clinical treatment medications at the time of death. The case has been reviewed by the hospital ethics committee.
23.6.2.1 Case Report
We present the case of a 49-year-old male patient who was admitted with an abdo-
minal pain and bloating for 38 h after overeating. He had history of pancreatitis. 
Admission examination revealed that the patient did not have fever (36.7 °C, axil-
lar), the pulse rate was 142 bpm, the respiratory rate was 22 bpm, the blood pres-
sure was 134/94 mmHg, and the oxygen saturation was 97%. The left mid-upper 
abdominal part was tender, no rebound pain or muscle tension. The results of the 
laboratory tests were showed as follows: blood routine showed WBC 21.78 × 10⁹ g/L, 
N 87%, Hb 144 g/L, PLT 68 × 10⁹ g/L. Blood biochemical indicators showed 
AMS2379U/L, LPS 1866 U/L, ALT 30.1 U/L, AST 76.5 U/L, TBIL 48.5 umol/L, 
DBIL 47.2 umol/L, GGT 90 U/L, UREA 12.9 mmol/L, CRE 220 umol/L, GLU 
26.15 mmol/L. Coagulation function showed APTT 31.3S, PT 17.6S, TT 13.1S, 
FIB 6.95 g/L, INR 1.63, d-dimer 4516 ng/mL. Inflammation indicators showed 
CRP 30.18 mg/dL and PCT 88.17 ng/mL. Abdominal CT demonstrated signs of 
acute pancreatitis. The patient was given symptomatic treatments such as acid inhib-
ition, enzyme inhibition, anti-infection, fluid replacement, hypoglycemia, and 
continuous hemofiltration. Three hours after admission, the patient developed 
unconsciousness, pale face, and progressive decrease in blood pressure. He was 
given rescue treatment, but eventually he failed to recover.

23.6.3 Review and Treatment

23.6.3.1 Etiology and Inducement
The common causes of acute pancreatitis are mainly gallstones and alcohol misuse. 
Other factors include hypertriglyceridemia or hypercalcemia, trauma, autoimmune 
diseases, endoscopic retrograde cholangiopancreatography (ERCP), steroids, drugs, 
and genetic factors [109–111]. Smoking is associated with nonbiliary acute pancre-
atitis [112]. Severe acute pancreatitis is associated with obesity and abdominal fat 
content. Abdominal obesity rather than systemic obesity is an independent risk fac-
tor for the development of acute pancreatitis [113]. Common precipitating factors 
for AP include alcoholism, overeating, excessive fatigue, emotional agitation, 
excessive stress, strenuous exercise, and consumption of cold and frozen drinks.

23.6.3.2 Lethal Mechanism
The mechanism of sudden death caused by acute pancreatitis is unclear. Current 
reports indicate that it may be related to the following factors:

Shock
Hypovolemic shock from acute pancreatitis is one of the causes of sudden death 
[114]. The possible mechanism is that pancreatic hemorrhage and necrosis release 
bradykinin, histamine, and other vasoactive substances to damage the pulmonary 
microvascular endothelium. Capillary permeability is increased, which promotes 
the exudation of a large amount of body fluids into the abdominal cavity and retro-
peritoneal space. The medium dilates small blood vessels, which causes a rapid 
decrease in the blood volume, and eventually leads to hypovolemic shock.
Acute Respiratory Distress Syndrome (ARDS)
Acute pancreatitis complicated by ARDS involves intricate mechanisms, including multiple levels of inflammatory waterfall, coagulation, and fibrinolytic system imbalance, and the activation of pancreatic enzymes. These levels are interconnected in a complex network. (1) The inflammatory mediators caused by pancreatic hemorrhage and necrosis can trigger a waterfall-like cascade through “trigger action.” A large number of inflammatory factors promote the accumulation and activation of inflammatory cells in lung tissue, aggravate lung tissue damage, and cause ARDS [115, 116]. (2) Pulmonary vascular injury caused by active trypsin: normally, trypsin inhibitors can inhibit the activation process of proteolysis. With an increase of trypsin in the blood circulation, trypsin inhibitors decrease, which can cause active trypsin to activate the kallikrein system and damage the pulmonary blood vessels. Active trypsin initiates the intravascular coagulation process, which promotes fibrin microthrombosis, involving pulmonary microcirculation, leading to ARDS. Autopsy studies have shown that fibrinoid thrombosis can be seen in the blood vessels of the lung tissue of patients with acute pancreatitis [117]. (3) Alveolar collapse caused by phospholipase: pancreatic lecithin is elevated in the serum of patients with hemorrhagic necrotizing pancreatitis. Lecithin is a major component of alveolar surfactants and plays an important role in exercising normal lung function. Lecithinase can accelerate the degradation of lecithin, reduce the activity of alveolar surfactants, atrophy of alveoli, and ARDS appears. At the same time, ARDS can aggravate the process of acute pancreatitis, form a vicious circle, and can affect other organs, eventually leading to MODS.

Arrhythmia
(1) Enzymes and toxic substances released by pancreatic hemorrhage and necrosis directly damage myocardial cells. (2) Insufficient myocardial perfusion due to low blood volume. (3) Electrolyte disorders, hypokalemia, hypocalcemia, hypomagnesemia, etc. can induce severe arrhythmias and ventricular fibrillation, leading to sudden death.

23.6.3.3 Diagnosis
Anyone with epigastric pain, inexplicable shock, or elevated hematuria amylase should consider the possibility of acute pancreatitis. According to the revised Atlanta Classification, the diagnostic criteria for acute pancreatitis are: (1) abdominal pain (acute onset of persistent and severe epigastric pain, often radiating to the back), (2) serum amylase (or lipase) at least three times the upper limit of normal, and (3) abdominal imaging examination (CT, MRI, and ultrasonography) is consistent with the imaging changes of acute pancreatitis. Acute pancreatitis can be diagnosed by having two of the above three criteria [109, 118].

Clinical Manifestations
Abdominal pain is the main symptom of acute pancreatitis. It is located in the epigastrium and periumbilical regions and often radiates to the back. Most of them are abrupt onset and constant. Nausea, vomiting, and abdominal distention are also frequent complaints. Fever often results from SIRS, secondary bacterial or fungal
infection of necrotic pancreatic tissue. Fever and jaundice are more common in biliary pancreatitis. The clinical manifestations of acute pancreatitis leading to sudden death are diverse, and can also be manifested as transient death, death during sleep, death after sudden screaming, and death after coma. Due to the short time from the onset to death, there is probably no typical severe abdominal pain of acute pancreatitis in the clinic. Cases of sudden death because of acute pancreatitis have been reported in the past where diagnosis could not be made until autopsy [119].

**Imaging**

Ultrasound examination within 24–48 h at the beginning of the onset can initially determine the morphological changes of the pancreas and contribute to identify the biliary tract disease [120]. However, gas accumulation in the gastrointestinal tract during acute pancreatitis decreases the accuracy. Contrast-enhanced CT (CECT) scan is recommended as the standard imaging method for diagnosing acute pancreatitis. CECT diagnosis about 1 week after the onset is more valuable and can effectively distinguish the range of fluid accumulation and necrosis. CECT is the gold standard for diagnostic imaging to help establish disease severity [121]. However, the predictive accuracy of CT scoring systems for severity of acute pancreatitis is similar to that of clinical scoring systems. Therefore, it is not recommended to only evaluate the degree of severity of acute pancreatitis during initial admission [122]. In addition, an early CT scan does not show an alternative diagnosis, help with the distinction of interstitial versus necrotizing pancreatitis, or provide evidence of an important complication. An early CT scan is recommended when there is a clinical doubt about the diagnosis of acute pancreatitis, and other life-threatening disorders have to be excluded. In addition, MRI can also assist in the diagnosis of acute pancreatitis.

**Etiological Diagnosis**

The etiology of acute pancreatitis should be determined using detailed personal (i.e., previous pancreatitis, known choledolithiasis, alcohol intake, medication and drug intake, known hyperlipidemia, trauma, and recent invasive procedures such as endoscopic retrograde cholangiopancreatography (ERCP)) and family history of pancreatic disease, physical examination (i.e., body mass index (BMI)), laboratory serum tests (i.e., liver enzymes, blood lipid, calcium, virus, autoimmune marker, and tumor marker (CEA, CA19-9)), and imaging (i.e., right upper quadrant ultrasonography, CECT, magnetic resonance cholangiopancreatography (MRCP), ERCP, ampulla papillary sphincter pressure measurement, and pancreatic exocrine function detection) [117].

**Graded Diagnosis**

The 2012 Revision of the Atlanta Classification Criteria divided AP into the following three categories: mild acute pancreatitis (MAP): not accompanied by organ failure or local or systemic complications; moderate severe acute pancreatitis (MSAP): accompanied by transient organ failure (<48 h) or local or systemic complications; and severe acute pancreatitis (SAP): accompanied by persistent organ failure (>48 h). The diagnostic criteria for organ failure are based on the modified Marshall
scoring system. Any organ score ≥2 points can be defined as organ failure [125]. Several scoring systems, such as Rason score system, Bedside Index for Severity in Acute Pancreatitis (BISAP), and modified CT Severity Index (MCTSI) score, have been developed to evaluate the severity of AP and promote clinical decision [122]. MCTSI score uses CT findings to judge the severity of AP, but early CT study can underestimate the severity of the disease [123, 124]. Rason score has 11 indicators including clinical factors, laboratory testing, response to fluid resuscitation, etc. It is cumbersome and not routinely used. BISAP score has five indicators and can be used at any time within 48 h of admission, which is relatively simple and effective for clinician.

23.6.3.4 Treatment
The current treatment model for AP is a combination of internal medicine and multidisciplinary treatment.

Fluid Resuscitation
Insufficient blood vessel content is the most prominent pathophysiological change in the early stage of acute pancreatitis. Fluid resuscitation is the cornerstone of early treatment. The 2018 AGA guidelines recommend the use of a target-oriented method for fluid management [126]. Targeted therapy is defined as the titration of intravenous fluids to specific detectable clinical and/or biochemical indicators, such as heart rate, mean arterial pressure, central venous pressure, urine output, BUN, HCT, etc. The types of infusions include lactated Ringer’s solution, normal saline, and colloid. At present, there is no high-quality evidence to prove that the recovery effect of lactated Ringer’s solution is better than that of normal saline. Expansion with hydroxyethyl starch is not recommended because it can increase kidney damage in patients with sepsis [127].

Organ Function Maintenance
(1) Treatment of acute lung injury or respiratory failure: in severe acute pancreatic pancreatitis, oxygen inhalation through nasal tube or mask should be given to maintain oxygen saturation above 95%. Patients’ blood gas analysis results should be monitored dynamically. When the disease progressed to ARDS, treatment strategies include mechanical ventilation and the use of high-dose, short-range glucocorticoids, and bronchoalveolar lavage under conditions [128]. (2) Treatment of acute kidney injury or renal failure: the treatment of acute renal failure is mainly supportive treatment, stable hemodynamic parameters, and dialysis. The indication of continuous renal replacement therapy (CRRT) is associated with acute renal failure, or the urine output ≤0.5 mL/kg/h; early with two or more organ dysfunction; SIRS with tachycardia, shortness of breath, the effect is not obvious after general treatment; with severe water and electrolyte disorders; and with pancreatic encephalopathy (PE). Combined with continuous venous-venous hemofiltration (CVVH) and continuous plasma filtration adsorption (CPFA) can be chosen [129]. (3) For SAP patients, special attention should be paid to maintaining the intestinal function. Because the stabilization of the intestinal mucosal barrier has an important role in reducing systemic complications, it is necessary to closely observe abdominal signs and defecation, monitor changes in bowel sounds, and give early
intestinal motility drugs, including rhubarb, magnesium sulfate, lactulose, etc., and use glutamine preparations to protect the intestinal mucosal barrier. Where conditions permit, early diet or enteral nutrition is important to prevent intestinal failure. Probiotics can regulate intestinal immunity and correct intestinal flora imbalance, thereby restoring the intestinal microecological balance. However, it is still controversial whether patients with severe acute pancreatitis should be treated with probiotics.

**Nutritional Support**
AGA recommends oral feeding of patients with acute pancreatitis as early as possible (within 24 h of onset). And enteral nutrition rather than parenteral nutrition is recommended for patients who cannot eat orally [118]. Enteral tube feeding should be the primary therapy in patients with predicted severe acute pancreatitis who require nutritional support but cannot eat. Glutamine should be the supplement. For patients with hyperlipidemia, fat supplementation should be reduced. When performing enteral nutrition, you should pay attention to whether the symptoms and signs of pancreatitis such as abdominal pain, intestinal paralysis, and abdominal tenderness are aggravated, and regularly test the electrolytes, blood lipids, blood glucose, total bilirubin and albumin, blood routine, and renal function, in order to evaluate the body’s metabolism and adjust the amount of enteral nutrition [109]. Short peptide preparations can be used first, and then gradually transition to whole protein preparations. The enteral nutrition solution should be selected according to the patient’s blood lipid and blood glucose.

**Drug Treatment**
The drug treatment of acute pancreatitis includes the inhibition of pancreatic exocrine and pancreatin inhibitors, adequate analgesia, and the application of antibiotics. At present, there is no breakthrough in drug treatment.

**Minimally Invasive Treatment**
In recent years, minimally invasive technology has developed rapidly and has gradually become the preferred intervention method for complications such as pancreatic necrosis infection and pancreatic pseudocyst. Currently, minimally invasive step-up therapy is considered the standard treatment for infectious pancreatic necrosis (IPN) [130]. Minimally invasive step-up therapy can be divided into two categories: (1) percutaneous retroperitoneal minimally invasive step-up therapy; (2) minimally invasive step-up therapy by stomach and/or duodenum. A large-scale retrospective study in 2016 compared the clinical prognosis of percutaneous retroperitoneal minimally invasive debridement therapy with open necrotic tissue wound surgery. Percutaneous retroperitoneal minimally invasive step-up therapy can reduce complications and mortality.

**Etiology Treatment**
(1) Endoscopic treatment of biliary pancreatitis: At present, ERCP is the first method to relieve biliary obstruction in patients with acute biliary pancreatitis. The IAP/APA guidelines point out that patients with biliary pancreatitis and cholangitis need emergency ERCP within 24 h [14]. For those without common bile duct
obstruction and cholangitis, early ERCP is not beneficial. In recent years, EUS has been used for the examination of common bile duct stones, and it has received increasing attention in the diagnosis and treatment of biliary pancreatitis. It can find small bile duct stones that are difficult to diagnose by MRCP. The IAP/APA guidelines recommend cholecystectomy for patients with mild biliary pancreatitis during hospitalization [118]. Studies have shown that delaying cholecystectomy for several weeks increases the risk of recurrence (up to 30%). However, early cholecystectomy in patients with necrotizing pancreatitis will increase the incidence of infection, and surgery is required after pancreatitis has healed [105]. (2) The incidence of hypertriglyceridemia pancreatitis is gradually increasing. Because HTGP is prone to exacerbation, the triglyceride (TG) level is positively correlated with the severity of the disease at the time of onset. Therefore, early lipid-lowering treatment may reduce the severity of the disease and improve the prognosis of patients with hypertriglyceridemia. The current early lipid-lowering programs can be divided into two categories: noninvasive drug treatment (insulin, heparin, etc.) and invasive blood purification treatment (plasma replacement, hemofiltration, etc.) [130].

23.6.4 Discussion

Acute pancreatitis, requires prompt treatment. In the above case, the patient suffered from abdominal pain due to overeating 38 h ago, but failed to pay attention because of previous pancreatitis. He did not fast, and even used nonsteroidal anti-inflammatory drugs (NSAID) on his own during abdominal pain, directly delaying the diagnosis and treatment. At the time of his consultation, he already had MODS and shock. At last, he was prone to sudden death. Because many acute pancreatitis are diagnosed after autopsy, the clinical attention to pancreatitis is insufficient.

23.6.5 Conclusion

Acute pancreatitis is one of the most common causes of sudden death in the digestive system. It has rapid onset, many complications, and a high degree of severity. But it is often confused with surgical acute abdomen and other digestive diseases of internal medicine. Once doctors ignore it, it is prone to become severe and even causes sudden death. We share the death case to let everyone know about the danger of acute pancreatitis.

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