GASTROINTESTINAL NON-INFECTIOUS COMPLICATIONS IN PATIENTS ON PERITONEAL DIALYSIS

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NEINFEKTIVNE GASTROINTESTINALNE KOMPLIKACIJE KOD BOLESNIKA NA PERITONEUMSKOJ DIJALIZI

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ABSTRACT

Gastrointestinal complications are common among patients on peritoneal dialysis. Risk factors for the development of gastrointestinal complications in this patient population include: toxic effects of uremic toxins, frequent use of nonsteroidal anti-inflammatory drugs, Helicobacter pylori infection, angiodysplasia, increased intra-abdominal pressure, use of bioincompatible solution for peritoneal dialysis, increased glucose in solutions for peritoneal dialysis, secondary hyperparathyroidism (hypercalcemia), a disorder of lipid metabolism (hypertriglyceridemia), and the duration of peritoneal dialysis treatment. The most important non-infectious gastrointestinal complications in patients on peritoneal dialysis are: gastrointestinal bleeding, herniation and leaking of the dialysate from the abdomen (increased intra-abdominal pressure), impaired lung function (intra-abdominal hypertension), acute pancreatitis, and encapsulating sclerosis of the peritoneum. Intra-abdominal hypertension is defined as IAP ≥ 12 mmHg. Pouring the peritoneal dialysis solution leads to increased intra-abdominal pressure, which results in the development of hernias, pleuro-peritoneal dialysate leakage (hydrothorax), and restrictive pulmonary dysfunction. Risk factors for the development of acute pancreatitis in this patient population include: uraemia, secondary hyperparathyroidism with hypercalcemia, hypertriglyceridemia, features of the peritoneal dialysis solution (osmolarity, acidity, glucose, chemical irritation, and calcium in the solution for peritoneal dialysis lead to "local hypercalcemia"), toxic substances from the dialysate, the bags and tubing, and peritonitis and treatment of peritonitis with antibiotics and anticoagulants. Encapsulating sclerosis of the peritoneum is rare and is the most serious complication of long-term peritoneal dialysis. It is characterized by thickening of the peritoneum, including cancer, and signs and symptoms of obstructive ileus. Diagnosis is based on clinical, laboratory and radiological parameters. Encapsulating sclerosis of the peritoneum can be indicated by an AR-CA-125 concentra-

SAŽETAK

Gastrointestinalne komplikacije se često javljaju kod bolesnika koji se leče peritoneumskom dijalizom. U faktore rizika za razvoj gastrointestinalnih komplikacija u ovoj populaciji bolesnika spadaju: toksično dejstvo uremijskih toksina, česta upotreba nesteroidnih antiinflamatornih lekova, infekcija helikobakterom pilori, angiodisplazija, povećan intraabdominalni pritisak, bioinkompatibilni rastvor za peritoneumsku dijalizu, povećan sadržaj glukoze u rastvorima za peritoneumsku dijalizu, sekundarni hiperparatireoidizam (hiperkalciemija), poremećaj metabolizma lipida (hipertrigliceridemija), dužina lečenja peritoneumskom dijalizom. Najznačajnije neinfektivne gastrointestinalne komplikacije kod bolesnika koji se leče peritoneumskom dijalizom su: gastrointestinalno krvarenje, hernije i oticanje dijalizata iz abdomena (povećan intraabdominalni pritisak), poremećaj funkcije pluća (intraabdominalna hipertenzija), akutni pankreatitis i inkapsulirajuća skleroza peritoneuma. Intraabdominalna hipertenzija se definiše kao IAP ≥ 12 mmHg. Ulivanje rastvora za peritoneumsku dijalizu dovodi do povećanja intraabdominalnog pritiska, a to za posledicu ima razvoj hernija i pleuro-peritoneumsko oticanje dijalizata (hidrotoraks), restriktivni poremećaj funkcije pluća i hernije. U faktore rizika za razvoj akutnog pankreatitisa u ovoj populaciji bolesnika spadaju: uremija, sekundarni hiperparatireoidizam sa hiperkalciemijom, hipertrigliceridemija, karakteristike rastvora za peritoneumsku dijalizu (osmolarnost, kiselost, sadržaj glukoze, hemijska iritacija, kalcijum u rastvoru za peritoneumsku dijalizu dovodi do "lokalne hiperkalciemije"), toksične supstancije iz dijalizata, kesa i cevčica, peritonitis i lečenje peritonitisa antibioticima i antikoagulantnom terapijom (i.p. primena antibiotika i heparina). Inkapsulirajuća skleroza peritoneuma je retka, najozbiljnija komplikacija dugogodišnjeg lečenja peritoneumskom dijalizom, koja se karakteriše zadebljanjem peritoneuma, obuhvatanjem creva, simptomima i znacima opstruktivnog ileusa. Dijagnoza se postavlja na osnovu kliničkih, laboratorijskih i radioloških parametara. Koncentracija AR-CA-125 manja od 33 U/min

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tion of less than 33 U/min and a concentration of AR-IL-6 greater than 350 pg/min in the effluent of patients with ultrafiltration weakness. Treatment consists of stopping peritoneal dialysis, using anti-inflammatory (corticosteroids) and anticicatricial drugs (tamoxifen), while surgical treatment includes enterolysis and adhesiolysis.

Keywords: *gastrointestinal complications, peritoneal dialysis*

i AR-IL-6 veća od 350 pg/min u efluentu kod bolesnika kod kojih postoji slabost ultrafiltracije ukazuje na inkapsulirajuću sklerozu peritoneuma. Lečenje se sastoji u prestanku lečenja bolesnika peritoneumskom dijalizom, primeni antizapaljenskih (kortikosteroidi) i antiožiljnih lekova (tamoksifen), dok hirurško lečenje uključuje enterolizu i adheziolizu.

Ključne reči: *gastrointestinalne komplikacije, peritoneumska dijaliza*

INTRODUCTION

Gastrointestinal complications are common among patients suffering from chronic kidney disease, and uraemia and dialysis (hemodialysis, peritoneal dialysis) are risk factors for gastrointestinal complications in this patient population (1). The prevalence of gastrointestinal symptoms in patients suffering from chronic kidney disease, including patients treated with haemodialysis and peritoneal dialysis, is estimated to be 70-80% (1). The prevalence of gastrointestinal symptoms and complications increases during the time a patient is treated with dialysis (1).

Gastrointestinal symptoms

Depending on the presence or absence of organic disease in the gastrointestinal system, patient symptoms may be organic (associated with lesions of the gastrointestinal tract), and/or functional (such as psychological factors, visceral hypersensitivity, or altered mobility or motility of the gastrointestinal tract) (1). There are six different groups of functional gastrointestinal symptoms: oesophageal, gastroduodenal, bowel syndrome, functional abdominal pain, biliary, and anorectal (1). The most common gastrointestinal symptoms in patients on peritoneal dialysis are sickness, nausea, vomiting, abdominal pain, constipation and diarrhoea. Irritable bowel syndrome is also highly prevalent in this population of patients (11-33%) (1).

Gastroparesis, or prolonged gastric emptying, frequently occurs in patients suffering from chronic kidney disease and patients on peritoneal dialysis. Etiopathogenesis is not completely clear; the main symptoms are nausea, vomiting, loss of appetite and anorexia (1).

The prevalence of constipation is 10-20% in the general population, 29% in patients on peritoneal dialysis, and 63% in patients on haemodialysis. The main causes of constipation are reduced physical activity, reduced intake of foods rich in fibre, the use of a phosphate binder, and the presence of a number of co-morbidities, such as diabetes mellitus and cerebrovascular disease(1).

Gastrointestinal complications

Gastrointestinal bleeding

Gastrointestinal bleeding is a common complication in patients suffering from chronic kidney disease and in patients treated with renal replacement therapies (hemodialysis, peritoneal dialysis). Gastrointestinal bleeding can be from the upper and/or lower gastrointestinal tract. The main causes of bleeding from the upper gastrointestinal tract are mucosal erosions (toxic effects of uremic toxins and/or nonsteroidal anti-inflammatory drugs), ulcers of the stomach or duodenum (uremic toxins, nonsteroidal anti-inflammatory drugs, Helicobacter pylori infection) and angiodysplasia. The prevalence of Helicobacter pylori (*Helicobacter pylori*) is high and varies between 49-66%. Helicobacter pylori infection is diagnosed by a urea breath test, which has a reduced sensitivity and specificity in this patient population. Triple therapy (proton pump blockers, clarithromycin, amoxicillin or metronidazole) is used to treat the infection, and oesophagogastroscopy is used to assess the treatment. The main causes of bleeding from the lower gastrointestinal tract are angiodysplasia, diverticulosis (32%) and colon cancer. Colon diverticulosis and diverticulitis are common in patients with polycystic kidney disease in the general population (1). Depending on the clinical course, the gastrointestinal bleeding may be acute (hematemesis, melena, and/or rectorrhagia) or chronic (a positive stool test for occult blood) (1). Acute bleeding from the upper gastrointestinal tract is more common in patients with chronic kidney disease than in the general population (21 cases/1000 patients/year) (1). Acute bleeding from the upper gastrointestinal tract is a significant cause of mortality in these patients; it is responsible for 3-7% of all deaths in patients with end-stage chronic kidney disease (1). Among patients suffering from chronic kidney disease, the prevalence of positive occult blood tests is 19% (1). Angiodysplasia is the most common cause of bleeding in the upper and lower gastrointestinal tracts. The use of antiplatelet and anticoagulant therapy increases the risk of gastrointestinal bleeding in patients with angiodysplasia and chronic kidney disease (1).

Intra-abdominal hypertension/abdominal compartment syndrome

Normal intra-abdominal pressure (IAP) is defined as 5-7 mmHg and is 9-12 mmHg in obese patients (9). Intra-abdominal hypertension (IAH) is defined as an IAP value ≥ 12 mmHg (9, 10). Depending on the level of IAP, there are four categories of IAH: grade I: IAP = 12-15 mmHg,

grade II: IAP = 16-20 mmHg, grade III: 21-25 mmHg and grade IV: IAP 25 mmHg (9, 10). Abdominal compartment syndrome (ACS) is defined as an IAP of > 20 mmHg and is associated with the dysfunction of a new organ or organ system with or without APP < 60 mmHg. Abdominal pressure perfusion (APP) = MAP - IAP (9, 10). ACS can be primary (intra-abdominal cause) or secondary (extra-abdominal cause). IAP values of 12-20 mmHg affect the function of organs, including the kidneys (9, 10). According to the *WSACS* (*World Society of the Abdominal Compartment Syndrome*) conditions associated with IAH and ACS include conditions with increased intra-abdominal volume (dilatation of the gastrointestinal tract, gastroparesis, stomach distention, ileus, volvulus, pseudo-obstruction of the colon, a tumour mass in intra-abdominal or retroperitoneal areas, ascites or haemoperitoneum, pneumoperitoneum (for example, during laparoscopic surgery), and peritoneal dialysis (peritoneal dialysis solution)) and conditions due to reduced elasticity of the abdominal wall (abdominal surgery, especially with tight, solid closing of the abdomen, bleeding into the wall of the abdomen, and surgical correction of large abdominal hernias), or a combination of both pathological conditions (obesity, sepsis, severe sepsis and septic shock, severe acute pancreatitis, complicated intra-abdominal infections, massive infusion therapy (resuscitation), and large burns) (9, 10). In patients with severe sepsis and septic shock, the incidence of IAH and ACS is 51-76% and 33%, respectively, while in patients with acute pancreatitis, the incidence of IAH and ACS is 59-84% and 25-56%, respectively (9). IAH is a risk factor for adverse outcomes in patients in intensive care units (9, 10).

The main clinical effects of IAH and ACS in patients who suffer from kidney failure are acute renal failure and increased pressure in the intrathoracic cavity (increased central venous pressure). The cut-off value of IAP for the development of acute renal failure is 12 mmHg (RIFLE classification for acute renal failure) (9). Due to the decreased venous return of blood from the abdomen (IAH), filling of the heart is decreased (cardiac preload), which results in reduced displacement of blood (reduced stroke volume/reduced cardiac output) and renal hypoperfusion (9, 10). Increased intrathoracic pressure leads to an increase in central venous pressure, which results in renal compartment syndrome (increased pressure in the venous system of the kidney and in the renal parenchyma) and reduced GFR (9, 10).

The main clinical consequences of increased IAP in patients on peritoneal dialysis are reduced compliance of the lungs (increased intrathoracic pressure), leaking of the peritoneal dialysis solution from the abdomen into the pleural space (hydrothorax) and the occurrence of hernias in weak areas of the abdominal wall (9, 10).

Leaking of the dialysate from the abdomen is classified as early (occurring within the first 30 days of placement of the catheter for peritoneal dialysis) and late (within the first year of catheter placement). Early dialysate leaks are designated as pericatheter dialysate leaks (dialysate flowing beside the catheter). Late dialysate leaks (into the abdominal wall, genital organs, or pleural space) are clinically manifested by increased body weight, swelling, and feelings of suffocation. There is also poor drainage of the dialysate and ultrafiltration weakness with late dialysate leaks (14). Risk factors for dialysate leakage are catheter placement technique, the catheter design, the period between the catheter placement and the initiation of peritoneal dialysis, the condition of the abdominal wall, and the condition of the diaphragm (14). Using the optimal technique to place a catheter for peritoneal dialysis, delaying initiation of peritoneal dialysis (10-14 days after placement of the catheter), gradually increasing the volume of the solution for peritoneal dialysis, and preserving the integrity of the diaphragm all prevent the development of dialysate leakage (14). Dialysate leaking from the abdomen into the pleural space results in the development of hydrothorax. Hydrothorax (transudate) is a rare complication of peritoneal dialysis that occurs as a result of dialysate leaking from the abdomen into the pleural space because of diaphragm defects or the transport of dialysate through the lymphatic vessels of the diaphragm (14, 15). The prevalence of hydrothorax in patients on peritoneal dialysis ranges from 1.6-6.0% (15). It occurs most often after the start of PD therapy. The right pleural space is predominantly affected, and the early clinical manifestations include feelings of suffocation, pleural pain, and decreased ultrafiltration (15). The diagnosis of peritoneal-pleural dialysate leakage can be aided by radiography of the heart and lungs (detecting pleural effusion), spirometry (identifying restrictive pulmonary dysfunction, pulmonary function tests to indicate a decreased vital capacity and reduced total lung capacity), thoracentesis (distinguishing transudates from exudates, indicating fluid peritoneal dialysis), computed tomography (CT) and nuclear magnetic resonance (NMR) peritoneography (detecting place and causes of dialysate leakage), scintigraphy peritoneum - Tc-99m DTPA (detecting leakage of dialysate) and video-assisted thoracoscopic surgery (VATS) (detecting defects of the diaphragm) (15, 16).

For the diagnosis of pleural effusion associated with peritoneal dialysis, we determine the concentration of glucose in the pleural fluid. A concentration of glucose in pleural fluid that is greater than 16.5 mmol/ l (> 300 mg/dl) indicates the presence of peritoneal dialysis solution (15). The cut-off value for the diagnosis of pleural effusions caused by peritoneal dialysis is a pleural liquid-serum concentration gradient greater than 2.77 mmol/ l (50 mg/ dl) (15). The treatment of pleural effusion associated with peritoneal dialysis (peritoneal-pleural dialysate leaking) is termination of PD therapy (4-6 weeks after cessation of peritoneal dialysis there is resolution of the effusion), video-assisted thoracoscopic surgery and talc pleurodesis (tetracycline and fibrin gel are equally used for pleurodesis) (16, 17, 18).

The treatment of IAH and ACS consists of placing a nasogastric tube in critically ill patients with pancreatitis, peritonitis, abdominal trauma and those who are postoperative (9, 10, 11). In patients with ileus (abdominal distension), prokinetic agents are applied, such as metoclopramide or erythromycin (9, 10, 11). In the case of ascites, paracentesis is used (9, 10, 11). In patients with marked hypervolemia (accumulation of fluid in the bowel wall, mesentery, retroperitoneum, abdominal cavity, or the abdominal wall), positive fluid balance (controlled infusion therapy), loop diuretics, and dialysis (ultrafiltration) are used (9, 10, 11). If reduction of IAP does not occur in patients after the administration of medication, surgical decompression of the abdomen is indicated if the IAP > 25 mmHg (APP < 50 mmHg (APP should be maintained at values > 60 mmHg)) and if there is new organ system failure (9, 10, 11).

Acute pancreatitis

Acute pancreatitis is an acute inflammatory disease of the pancreas caused by intracellular activation of pancreatic digestive enzymes (1, 5). The decomposition of pancreatic tissue stimulates a systemic activation of the coagulation, fibrinolytic, and complement systems, and the release of cytokines and reactive oxygen species leads to severe manifestations of systemic diseases, such as shock, acute renal failure, acute respiratory distress syndrome, and adult respiratory distress syndrome (5). The incidence of acute pancreatitis has dramatically increased in the last two decades. In the United States, severe acute pancreatitis is responsible for more than 200,000 hospitalizations annually (13). In 80% of cases, acute pancreatitis is mild; approximately 20% of patients develop a severe form of acute pancreatitis with local and systemic complications. The mortality rate of severe acute pancreatitis is high and amounts to approximately 30% (13).

Pancreatitis associated with cholelithiasis occurs in 45% of patients, and alcohol is responsible for acute pancreatitis in 35% of cases (5). In 10% of patients, there is idiopathic acute pancreatitis (unclear cause). Alcoholic pancreatitis is more common in people younger than 40 years of age. Cholelithiasis-associated pancreatitis is more common in women and those aged between 50 and 60 years (3:1 ratio). Hypercalcemia is also an important cause of acute pancreatitis in patients who are suffering from hyperparathyroidism (5).

The exocrine pancreas secretes 1500-2000 ml of fluid, 150-200 mmol $HCO3^-$/day and inactive precursors of amylolytic (amylase), lipolytic (lipase) and proteolytic (proelastase, chymotripsynogen) digestive enzymes. Trypsin is necessary to activate these digestive enzymes. Trypsin is created through the conversion of trypsinogen by the action of enterokinase, which is secreted by the mucosa of the duodenum (5). Several important factors in the development of acute pancreatitis are damage to the mechanisms that block the activation of proteolytic enzymes; permanently increased concentrations of calcium in the serum; increased pressure in the pancreatic channel (obstruction of the flow of pancreatic secretion due to edema, stones, spasms of the ampulla of Vater sphincter, disruption of small ductules of the pancreatic duct, and the spread of pancreatic juices into the pancreatic parenchyma); the return of duodenal contents in pancreatic duct (duodenal pancreatic reflux); the activation of trypsinogen under the influence of enterokinase and hypersecretion due to increased stimulation of muscarinic receptors associated with poisoning by organic phosphates or a scorpion bite (5). The destruction and degradation of the pancreatic tissue leads to a systemic activation of the coagulation system, the fibrinolytic system and the complement system. This results in the release of cytokines (TNFα, IL-1, IL-6, IL-8, and platelet-activating factor, PAF), and the reactive metabolite oxygen, which leads to systemic manifestations of the pancreatitis, such as a shock (increased permeability of the capillary walls, vasodilation, decreased contractility of the myocardium), acute renal failure, and acute respiratory distress syndrome (ARDS) (5).

There are two forms of acute pancreatitis: oedematous interstitial pancreatitis and necrotizing pancreatitis. Depending on the natural flow, there are two phases of acute pancreatitis: an early phase (in the first one to two weeks) and a late phase (in the following few weeks and months) (12). The majority of patients (80-90%) have acute interstitial oedematous pancreatitis (a diffusely enlarged pancreas) without the presence of necrosis in the parenchyma of the pancreas or in the peripancreatic tissue (12). Peripancreatic fluid collection, excluding pancreatic necrosis, can occur with this type of pancreatitis (12). With necrotizing pancreatitis there is necrosis of pancreatic parenchyma tissue and/or peripancreatic tissue. The presence of parenchymal tissue necrosis indicates a more severe form of acute pancreatitis. A CT scan of the abdomen with contrast is the gold standard for the diagnosis of pancreatic and peripancreatic necrosis in the first weeks of the disease (12). The necrotizing form of acute pancreatitis is often associated with infection, which is diagnosed on the basis of symptoms and signs of sepsis and laboratory parameters (CRP, procalcitonin). Percutaneous aspiration of necrotic pancreatic tissue with a thin needle is used to diagnose and determine the cause of the infection (bacteria or fungi). Infection can also occur secondarily after percutaneous, endoscopic, or operative intervention and is associated with increased morbidity and mortality (12).

The clinical picture depends on the type, stage and severity of acute pancreatitis. Epigastric abdominal pain, which spreads in the upper abdomen area below the ribs, is the dominant symptom of acute pancreatitis. The pain can be moderate or severe, constant or sporadic. Nausea and vomiting occurs in over 90% of patients. Other symptoms include bloating of the stomach, blueness in the umbilical area because of haemoperitoneum (*Cullen's sign*), and bluish-red, purple, or brown discoloration of the skin on

Table 1. *Ranson/Imrie* prognostic criteria for acute pancreatitis

At the reception or at the time of diagnosis
Age > 55 years
The number of leukocytes > 15.0 x 10^9/l
Hyperglycemia > 10 mmol/l
LDH in serum > 600 U/l
AST in serum > 100 U/l
During the first 48 hours of hospitalisation
Drop in hematocrit of > 10%
Hypocalcemia < 2.0 mmol/l
Increasing of urea for > 1.8 mmol/l
Sequestration of fluid > 4.0 liters
Hypoalbuminemia < 32 g/l
Hypoxemia < 60 mmHg (FiO2 0.2l)

Three or more positive criteria indicate severe acute pancreatitis.

the lateral areas of the abdomen (*Grey-Turner's sign*) (5). During the early stages of acute pancreatitis (approximately 1-2 weeks), systemic manifestations (acute renal failure, acute respiratory distress syndrome, and circulatory insufficiency) are associated with a systemic inflammatory response (SIRS) and anti-inflammatory syndrome (CARS) (12). The late stage can last several weeks or months and is characterized by systemic symptoms and signs of inflammation, local and systemic complications and/or transition to persistent organ failure (12).

After the diagnosis of acute pancreatitis, it is important to estimate its severity to establish the treatment and prognosis (12). There are three stages of severity in acute pancreatitis: mild (85%), moderately severe and severe. The definition of the severity of acute pancreatitis is based on the presence or absence of organ failure and local and systemic complications (12). Mild acute pancreatitis is characterized by the absence of organ failure and local/systemic complications (12). Moderately severe acute pancreatitis is defined as transient organ failure (organ failure that recovers within 48 hours) and/or the presence of local or systemic complications (12). Severe acute pancreatitis is characterized by the persistent failure of one or more organ systems (failure lasts longer than 48 h) (12).

The *Ranson/Imrie* score is used to assess the severity of acute pancreatitis (table 1) (5).

Persistent organ failure is defined as organ failure that lasts longer than 48 hours. For the detection of renal organ failure, the modified *Marshall System Score* is used. This score assesses the function of the three organ systems that are most affected in acute pancreatitis: the respiratory and cardiovascular systems and the kidneys (urinary system) (Table 2) (12).

Persistent organ failure is defined as a score ≥ 2 for a period longer than 48 hours for a single organ system (12). Transient organ failure is also important for the classification of moderately severe acute pancreatitis and is defined as a score ≥ 2 for at least 1 of the three body systems that is present for a period no longer than 48 hours (12).

The local complications include acute peripancreatic collection of fluid (APEC), pancreatic pseudocyst, acute necrotic collection (ANC) and limited necrosis or WON (*walled-off necrosis*) (12). APEC occurs in the acute phase of interstitial oedematous acute pancreatitis. It is not associated with necrotizing acute pancreatitis. If it persists for longer than 4 weeks it becomes a pseudocyst of the pancreas (12). A pancreatic pseudocyst is encapsulated, clearly limited by a wall or homogenous collection of liquid, and occurs 4 weeks after the beginning of interstitial oedematous pancreatitis (12). ANC is present in the first four weeks after the beginning of disease (intrapancreatic, extrapancreatic). It occurs as a result of pancreatic necrosis or necrosis of peripancreatic tissue, and it contains varying amounts of liquid and solid necrotic material and has no encapsulating wall (12). MRI and ultrasound are better for the detection of solid material within the cyst or necrotic cavity (12). Acute necrotic collection can be sterile but can also lead to its infection (13).

ANC is not considered a pancreatic pseudocyst because it contains solid material associated with tissue necrosis (12). After maturation, ANC becomes clearly limited by a wall - WON (thickened wall of the reactive tissue) (12). This develops at least 4 weeks after the beginning of necrotizing pancreatitis. There can be a lot of ANC and WON (12). Local complications prolong hospitalization, require interventions, and are important for the definition of moderately severe acute pancreatitis. Persistent or permanent abdominal pain, secondary or repetitive increases in the concentration of amylase or lipase serum levels, or-

Table 2. Modified Marshall Scoring System

Organ system	Score				
	0	1	2	3	4
Respiratory: PaO_2/FiO_2	> 400	301-400	201-300	101-200	≤ 101
Kidney: creatinine µmol/l	< 134	134-169	170-310	311-439	> 439
KV system: systolic blood pressure, *mmHg*	> 90	< 90 (in reply to fluid resuscitation)	< 90 (lack of response to fluid resuscitation)	< 90 pH < 7.3	< 90 pH < 7.2

gan failure or fever require prompt use of an abdomen CT scan with contrast in order to detect any complications (12). Systemic complications include functional disorder of the lungs, cardiovascular system and the kidney. These complications are the foundation for systemic inflammatory response syndrome (SIRS), which can occur in acute pancreatitis.

Patients with severe acute pancreatitis have a greatly increased risk of death (30-50%). If there is pancreatic or peripancreatic necrosis, the mortality rate increases to 80% (12).

The conventional diagnostic test for acute pancreatitis is measuring the concentration of amylase activity in the serum. Values that are at least 3 times greater than the upper limit of normal indicate acute pancreatitis (5). In patients with acute pancreatitis, amylase concentration in the serum increases within 2-3 hours, peaks within 12-24 h, and returns to normal after 3-5 days (5). The normal concentration of amylase in urine is 10-300 IU/l; values greater than 750 IU/L indicate acute pancreatitis. A concentration of serum lipase greater than 2 times the upper normal limit indicates acute pancreatitis. Lipase concentration in serum increases within 4-8 h, peaks after 24 hours, and normalizes after a week (5). In patients with acute pancreatitis, amylase concentration in the fluid of the peritoneum is more than 50.000 IU/l (5). Additional tests for acute pancreatitis include abdominal ultrasound, CT of the abdomen with contrast (the gold standard for the diagnosis of pancreatic necrosis and peripancreatic collection) and endoscopic retrograde cholangiopancreatography (ERCP) (acute pancreatitis caused by a small stone in the ampulla of Vater) (5). Based on the findings of the abdominal CT scan, severe acute pancreatitis is categorized into five stages, 0-4. The degree of pancreatic necrosis is also evaluated on the basis of an abdomen CT scan with contrast and defined by four categories. Based on these two scoring systems, the severity score of the CT index is calculated. An index score greater than 7 indicates a high morbidity and mortality in patients with acute pancreatitis (13).

All patients with severe acute pancreatitis and failure of at least one organ system (circulation, kidney, or lung) require admission to the Intensive Care Unit. The treatment consists of supportive therapy; infusion therapy provides an optimal haemodynamic and electrolyte status, the pancreatic and enteric stimulation is blocked by placing a nasogastric tube, and antibiotics are administered prophylactically (imipenem 500 mg IV every 8 h for 7-10 days, plus IV Fluconazole 400 mg/day) (13).

A significant complication of severe acute pancreatitis is acute renal failure (renal hypoperfusion, IAH: oliguria occurs when IAP ≥ 15 mmHg, and anuria occurs when IAP ≥ 30 mmHg). Fractional excretion of sodium (FE_{Na+}) > 1%, the concentration of sodium in the urine sample (U_{Na+}) > 40 mmol / l and fractional excretion of urea (FE of urea) ≥ 35% point to the development of acute tubular necrosis in patients with severe acute pancreatitis (5, 7). Treatment of acute renal failure in patients with severe acute pancreatitis includes the treatment of acute pancreatitis, IAH, ACS, and dialysis support therapy (5, 7). Continuous veno-venous-hemofiltration (CVVHF) is used as a nonrenal indication for the reduction of a systemic inflammatory response. High-volume CVVHF (HVHF) is used in the early stages of acute pancreatitis (within 72 h), and the test results show that it substantially reduces the concentration of inflammatory cytokines in the serum (TNFα, IL-1, IL-2, IL-6) (5, 7). With patients with severe acute pancreatitis, acute renal impairment and haemodynamic instability, continuous veno-venous haemodiafiltration (CVVHDF) is used (standard dose filtration rate: 20 ml/kg/h, high dose of filtration: 35 ml/kg/h). In patients who are haemodynamically stable, intermittent dialysis modalities, such as slow low-efficiency everyday dialysis (SLEDD) (6 times a week, 3 x per week) or standard haemodialysis (3 x week), can be administered. The ultrafiltration dose should be adjusted individually for each patient depending on their clinical condition (5, 7).

Acute pancreatitis in patients on peritoneal dialysis

Acute pancreatitis is an acute inflammatory disease of the pancreas that is not very common among patients on peritoneal dialysis. The incidence of acute pancreatitis in patients on peritoneal dialysis is 7/241 patients/year (1). Risk factors that increase the incidence of acute pancreatitis in this patient population include uraemia, secondary hyperparathyroidism with hypercalcemia, hypertriglyceridemia, different features of the solution used for peritoneal dialysis (osmolarity, acidity, glucose, chemical irritation, and calcium in solution for peritoneal dialysis leads to "local hypercalcemia"), the toxic substances from the dialysate, the bags and tubing, peritonitis and treatment of peritonitis with antibiotics and anticoagulants (i.e. applying of antibiotics and heparin) (table 3) (1, 5, 8).

The main symptoms of acute pancreatitis in patients on peritoneal dialysis are acute pain in the abdomen (100% of patients), nausea, vomiting (in 73% and 67% of patients), bloating of the stomach (7% of patients), and haemorrhagic effluent (approximately 20% of patients) (1, 5, 8).

Table 3. The most common risk factors for the development of acute pancreatitis in patients on peritoneal dialysis

Risk factors	The number of cases N(%)
Biliary lithiasis	10 (13.3)
Alcohol	4 (6.2)
Medications	8 (11.6)
Hypercalcemia	26 (34.7)
Hyperlipidemia	32 (43.2)
Hyperparathyroidism	25 (51.0)
Trauma/Surgery/Transplantation	5 (10)
Infection	2 (6.1)
Idiopathic	20 (27.4%)

The diagnosis of acute pancreatitis in patients on peritoneal dialysis is difficult because of the reduced sensitivity of laboratory parameters (biochemical tests include amylase and lipase in the serum) and because it overlaps with other syndromes, such as peritonitis. Serum amylase tests have been shown to have reduced sensitivity in patients on peritoneal dialysis with long-term icodextrin exchanges, because icodextrin reduces the activity and concentration of amylase in the serum. The concentration of amylase in the serum was found to be normal in 12.8% of acute pancreatitis episodes (8). Measuring the concentration of lipase in the serum has a higher diagnostic value for acute pancreatitis among patients on peritoneal dialysis who are using 7.5% solution of icodextrin (5, 6, 8). Increased concentration of amylase in the effluent of patients with acute abdominal pain being treated by peritoneal dialysis may indicate the development of acute pancreatitis in the absence of acute peritonitis (1, 5, 8). In addition to laboratory testing, the two most important examinations of the morphology of the pancreas are abdominal ultrasound and CT (1, 5, 8).

The majority of patients is treated conservatively by supportive therapy. The development of complications of acute pancreatitis, such as pancreatic abscess or necrosis, requires laparotomy (8). The mortality rate of patients on peritoneal dialysis for acute pancreatitis is 31.5% (8).

Encapsulating sclerosis of the peritoneum

Encapsulating sclerosis of the peritoneum (EPS) is rare and is the most serious complication of long-term peritoneal dialysis. EPS is characterized by thickening of the peritoneum, seizing of the small intestine, and the symptoms and signs of obstructive ileus (1, 2, 3). The prevalence of EPS in patients on peritoneal dialysis ranges from 0.5-7.3% and increases to 15.2% in patients receiving peritoneal dialysis treatment for more than 15 years (1, 2, 3).

Risk factors for the development of EPS include recurrent episodes of peritonitis, the absence of residual renal function, exposure of the peritoneum to solutions with a high concentration of glucose over a longer period of time, bioincompatible solutions for peritoneal dialysis (glucose, glucose degradation products, lactate in acid solution), treatment cessation of patients with peritoneal dialysis (switching to haemodialysis), the post-transplantation period in patients who were treated by peritoneal dialysis (use of blocking calcineurin), and trauma to the peritoneum (surgery) (1, 2, 3).

The pathogenesis of EPS is not fully understood. Increased production of transforming growth factor beta (TGFβ) and endothelial growth factor (VEGF) in fibroblasts of the peritoneum and neovascularization (formation of new blood vessels in the thickened peritoneum) have important roles in the thickening of the peritoneum (2, 3).

The symptoms and signs that indicate EPS include abdominal pain, abdominal bloating, nausea, vomiting, anorexia, constipation, loss of body weight, loss of ultrafiltration capacity (ultrafiltration weakness of the peritoneum), high transport characteristics of the peritoneum and intermittent bowel obstruction (small bowel obstruction) (1, 2, 3).

A high index of clinical suspicion is necessary to diagnose EPS. Diagnosis is based on clinical and radiological findings (abdominal ultrasound and CT). A CT scan of the abdomen can reveal thickening of the peritoneum, adhesions of the intestinal loops, signs of bowel obstruction and the presence of fluid collection in the abdomen (1, 2, 3). Treatment includes cessation of peritoneal dialysis, application of the anticicatricial drugs (tamoxifen), corticosteroids and immunosuppressive agents, nutritional support and surgical enterolysis and adhesiolysis (1, 2). Tamoxifen blocks the formation of TGFβ in the fibroblasts of the peritoneum and is administered at a dose of 10-80 mg/day (generally 40 mg/day). It is well tolerated; potential side effects are nausea, weakness, endometrial cancer and deep vein thrombosis (1, 2). Corticosteroids are used at a dose of 0.5-1.0 mg/kg/day (maximum daily dose of 80-100 mg), with a gradual dose reduction for 4-5 months. In addition to corticosteroids, patients receive azathioprine at a dose of 50 mg/day for 2-3 months (1, 2). In most clinical studies, corticosteroids have been administered at a dose of 0.5 mg/kg/day in combination with azathioprine at a dose of 1.5 mg/kg/day for 4 weeks. After treating the symptoms of the gastrointestinal tract, the dose of azathioprine is reduced to 75 mg/day, and the corticosteroid is reduced to 20 mg/day for several months (2). Corticosteroid doses of 50 mg/day can be applied in combination with mycophenolate mofetil at a dosage of 500 mg 2 x 1 during the two months (2).

In addition to the optimization of anti-inflammatory and anticicatricial therapy, trials of EPS are focused on the early detection of the inflammatory phase of EPS. Currently this is done through determination of the concentrations of CA-125, IL-6, TGFβ, and MMP-2 in the effluent. These biomarkers are associated with inflammation, remodelling of tissue, damage of the peritoneal membrane and increased transport through the peritoneal membrane (2). In patients with ultrafiltration weakness, an effluent concentration of less than 33 U/min of AR-CA-125 and greater than 350 pg/min of AR-IL-6 has a sensitivity of 70% and specificity of 89% in diagnosing EPS (2). Well-controlled clinical trials should confirm the importance of CA-125 and IL-6 concentrations in the effluent for diagnosing the inflammatory stage of EPS (2).

For patients with an increased risk of EPS, it is necessary to use prophylaxis, which involves tamoxifen 20-40 mg/day and low doses of corticosteroids (0.5 mg/kg/day) (2).

Regardless of the treatment, the mortality rate is high, between 20-93%, and in patients who are on peritoneal dialysis for more than 15 years, the mortality rate is almost 100% (1, 2).

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