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DIAGNOSIS AND TREATMENT OF NECROTIZING ENTEROCOLITIS IN PRETERM INFANTS

Matniyova Zaynab Tukhtabayevna
Bukhara State Medical Institute, Bukhara, Republic of Uzbekistan
zaynabmatniyazova1@gmail.com

Annotation: Necrotic enterocolitis remains one of the main causes of morbidity and mortality mainly among premature infants with low and extremely low body weight. The percentage of newborns with necrotic enterocolitis tends to increase in recent years, which is associated with the intensive development of neonatology and resuscitation. Diagnosis in the early stages of the disease in small children is extremely difficult. Active study of the most significant diagnostic factors in the early stages of the disease is one of the first tasks of neonatologists. X-ray examination is the most reliable diagnostic method for the appearance of a clinical picture of necrotic enterocolitis. With the development of the surgical stage of the disease, the mortality rate among premature infants with extremely low body weight increases sharply. Choosing the most optimal method of surgical treatment in such children remains an important task for pediatric surgeons.

Key words: premature infants with low and extremely low body weight, necrotic enterocolitis.

Introduction
Neonatal necrotic enterocolitis is a non-specific inflammatory disease caused by infectious agents against the background of immaturity of local defense mechanisms and hypoxic-ischemic damage to the intestinal mucosa, prone to generalization with the development of a systemic inflammatory reaction. In 1944, W. Heinrich (Switzerland) described 62 cases of necrotic enterocolitis in newborns; all children died, the etiology of the disease is not disclosed (cit. [2]). Only in 1969 J. Lloyd in Detroit suggested that the development of the disease is associated with neonatal hypoxia [3]. Until now, the cause and pathogenesis of this terrible disease have not been fully studied, so, by definition, DCI oherty (2002), neonatal necrotic enterocolitis — an acute necrotic intestinal syndrome of unclear etiology. In its pathogenesis, hypoxia and disruption of mesenteric blood flow leading to disruption of the barrier function of the intestinal mucosa, translocation of microbes into the bloodstream, inflammation triggering a cascade of cytokine reactions, mucosal ulceration, necrosis and perforation should be considered as the leading link [2, 4-10]. This raises a number of questions: does ischemia trigger all the processes described above, or does inflammation, which causes vasoconstriction through pro-inflammatory cytokines and then leads to perforation of the intestinal wall?

Diagnosis: not a single case of intrauterine necrotizing enterocolitis has been described (in the presence of chronic intrauterine fetal hypoxia) and, finally, if the primary cause is ischemia, why does the disease develop on the 7th-14th day of the child's life, and not at the most critical point of ischemia — in utero, intranatally, and in the early neonatal period [2, 11]. The incidence of necrotic enterocolitis in newborns, according to various authors, ranges from 0.3 to 3 per 1000 children. The number of newborns with necrotizing enterocolitis tends to increase in recent years[1, 2, 4, 5, 7, 12-15]. This is due to the intensive development of neonatology and resuscitation, which makes it possible to care for very premature babies. It is known that the incidence of pathology and the level of mortality are directly proportional to the degree of maturity of the newborn. The vast majority (90 %) of these infants are preterm infants with a body weight of less than 1500 g, which is why
necrotizing enterocolitis is called "preterm survivors 'disease". This is confirmed by the fact that in countries where the birth rate of premature babies is low (Japan, Switzerland), this disease is less common — with a frequency of 2.1% among all children admitted to neonatology intensive care units [16]. Currently, the mortality rates are not much better than when the disease was first described by W. Thus, despite the intensive joint efforts of neonatologists, pediatric surgeons, and anesthesiologists-resuscitators, as well as the development of modern technologies for nursing and treating newborns, the mortality rate ranges from 28 to 60 % [2]. At the moment, there are several classifications of necrotic enterocolitis. The most commonly used classification is M. Bell in modification M. Walsh and R. Kliegman [1, 4, 7, 9, 12, 13, 17]. Stages of necrotic enterocolitis: stage 1 - "suspected necrotic enterocolitis" or prodromal: 1A-characterized by the following symptoms: unstable body temperature, apnea, bradycardia, lethargy; slight bloating; radiologically, intestinal loops look normal or slightly expanded, horizontal levels may appear; 1B-characterized by an admixture of bright red blood in the feces; stage 2 - "obvious necrotic enterocolitis" is characterized by two components: 2A — "reversible stage", the appearance of signs of stage 1 + intestinal paresis + radiologically intestinal pneumatosis; 2B — "irreversible stage", the same symptoms + radiologically gas in the portal system; stage 3 — "progressive necrotic enterocolitis": 3A — signs of peritonitis, expansion of intestinal loops, multiple horizontal levels, pneumatosis of the intestinal wall; 3B-generalized peritonitis with its complications (disseminated intravascular coagulation syndrome, multiple organ failure syndrome, sepsis), pneumoperitoneum. Early symptoms of the disease are non — specific and variable-from signs of intolerance to enteral nutrition to a catastrophic course with a clinical picture of sepsis, shock and peritonitis. CNS depression syndrome, apnea, and signs of impaired tissue perfusion (positive white spot symptom, peripheral cyanosis, acidosis, hyperglycemia, and temperature instability) dominate. Flatulence, delayed evacuation of gastric contents, diarrhea, stool with an admixture of blood are common. The progressive process is manifested by erythema and swelling of the abdominal wall, increasing tension of the abdominal muscles. In premature newborns with extremely low body weight, the clinical picture is even more non-specific [2, 5, 7, 9, 12, 13, 16,18]. When a clinical picture of necrotizing enterocolitis appears, X-ray examination is the most reliable diagnostic method that reflects the stages of the process in the intestine. Suspicion of the development of the disease involves a dynamic X-ray examination of the patient during the first day with an interval of 6-8 hours, then the images are performed according to the indications. Radiological signs of necrotizing enterocolitis: uneven swelling of the intestinal loops, pneumatosis of the intestinal wall (cystic or linear), gas in the portal system of the liver, the presence of a hypostatic loop of the intestine, pneumoperitoneum, the presence of fluid in the abdominal cavity. Pneumatosis and gas in the portal system of the liver are the most common signs of necrotizing enterocolitis. Stage 1 is characterized only by increased pneumatization of intestinal loops. With the progression of the disease (stage 2), an increase in the distance between the intestinal loops is determined, which indicates the appearance of edema of the intestinal wall and an increase in the phenomena of peritonitis. Intestinal loops are clearly contoured, due to increased filling, their contours are straightened due to edema and rigidity. Intestinal pneumatosis (accumulation of gas bubbles in the thickness of the intestinal wall tissues) is one of the characteristic signs of necrotizing enterocolitis. Microscopically, gas bubbles are determined by interstitial tissue of the intestinal wall, as well as along the course of lymphatic vessels and small branches of the portal vein, can be detected macroscopically under the visceral peritoneum. Pneumatosis usually associated with local infarction of the intestinal wall and areas of preperforation and perforation. Usually this phenomenon is accompanied by symptoms of generalized peritonitis. This sign is absent only in 10 % of patients with a confirmed diagnosis of necrotizing enterocolitis. Radiologically, there are two types of pneumatosis: cystic and linear. The cystic form has the form of granules or foam and is represented by gas in the submucosal layer. Linear pneumatosis may be present...
Together with cystic or develop immediately after it. Small gas bubbles collect in the muscle or subserous layer in the form of a thin straight or curved line. With the progression of intestinal pneumatosis, gas bubbles are detected along the portal vein, which also reflects the presence of transmural infarction. Gas in the portal system of the liver is associated with a poor prognosis. In cases of total intestinal damage, gas in the portal system of the liver is present in 61% of patients. The presence of a gas-stretched "motionless" intestinal loop on a series of radiographs indicates its necrosis (stage 3 of necrotizing enterocolitis). Such a loop can be a single one, less often it is represented by a conglomerate in any part of the abdominal cavity. Polypositional X-ray examination of the patient allows differentiating increased gas filling of intestinal loops from their ischemic lesion. Perforation of the intestine or stomach is manifested by a decrease in pneumatization of intestinal loops and the appearance of free gas in the abdominal cavity. On radiographs, free gas is defined as a "sickled" under the right and left dome of the diaphragm in the patient’s vertical position, accumulation under the anterior abdominal wall on lateral radiographs in the patient’s supine position, a "soccer ball" symptom (accumulation around the sickle-shaped ligament of the liver) in a frontal image in the supine position. Free gas in the abdominal cavity is detected only in 40% of cases of all existing perforations. The absence of free gas in the abdominal cavity on the radiograph can be observed in the case of a "covered" perforation, an atypical localization of the hole in the omentum sac. Pneumoperitoneum can occur without perforation of the hollow organ in weakened patients, many of whom were on artificial ventilation due to pulmonary pathology (barotrauma leads to rupture of the alveoli and air penetration through the mediastinum into the abdominal cavity). This situation occurs in 10-15% of cases. This point should be taken into account in the differential diagnosis of necrotizing enterocolitis. Ascites in the form of darkening in the sloping areas of the abdominal cavity accompanies the development of the infectious process. X-ray signs of fluid in the abdominal cavity include: - severe bloating with reduced gas filling intestinal loops; - concentration of gas-filled intestinal loops in the center of the abdominal cavity - increasing the distance between the intestinal loops. Gastric dilation and dilatation of the large intestine are associated with the effect of toxic agents (bacterial toxins) on the affected gastrointestinal mucosa, as well as pylorus obstruction on the background of edema. The use of X-ray contrast examination of the passage through the gastrointestinal tract with its slowing down and determination of the "dumb" loop, as well as irrigation to detect signs of edema of the intestinal walls and ulcers on the mucosal surface is limited due to the high risk of complications [1, 4, 9, 12]. Recently, much attention has been paid to the increase in intra-abdominal pressure in progressive necrotic enterocolitis and the development of intra-abdominal hypertension syndrome. In 2004, at the WSACS (World Society of the Abdominal Compartment Syndrome) conference, intraabdominal hypertension was defined as follows: this is a steady increase in intra-abdominal pressure up to 12 mm Hg. and more, which is recorded for at least three standard measurements with an interval of 4-6 hours. Intraabdominal hypertension is the prodromal phase of the development of abdominal syndrome (or intraabdominal hypertension syndrome). Intraabdominal hypertension syndrome is a multi-organ failure caused by an increase in intra-abdominal pressure in a limited space, which leads to circulatory disorders, hypoxia and ischemia of organs and tissues located in this space, contributing to a pronounced decrease in their functional activity until its complete cessation [7]. An informative diagnostic method is ultrasonography, which allows you to detect the expansion of intestinal loops, delamination and thickening of the intestinal wall, free fluid and gas in the abdominal cavity. Ultrasound examination (US) in the Doppler mode allows you to assess blood flow in the vessels of the superior mesenteric artery basin and in some cases to make a clear gradation of the stages of necrotic enterocolitis, the transition to necrosis of the intestinal wall, which requires active surgical tactics [5, 6, 9, 19]. Simple implementation, good tolerability, and the absence of ionizing radiation make this diagnostic
method indispensable for solving the problem of surgical intervention [4, 20,31,32,33]. In 1984, C. Merritt, J. Goldschnuth, and M. Sharp described the presence of gas in the portal vein in 12 newborns with necrotic enterocolitis diagnosed by ultrasound. 5 of these children had no X-ray signs of necrotizing enterocolitis. The authors described two features characteristic of this pathology: highly echogenic particles (microbubbles) in the portal vein and highly echogenic "plaques" in the hepatic parenchyma. Ultrasound should be performed in all patients, especially those with non-specific radiological or doubtful clinical signs for necrotizing enterocolitis. Using this method, you can also diagnose the localization of free fluid in the abdominal cavity in order to perform paracentesis.[2, 6, 9, 18, 21, 22]. Among diagnostic laboratory tests, the most constant and informative are changes in the hemogram (leukocytosis / leukopenia, a shift in the leukoformula left, thrombocytopenia), increased C-reactive protein, acidosis, electrolyte imbalance [1, 8-10, 14, 16, 23, 24]. Unfortunately, all of them are not specific to this pathology. According to foreign authors, the role of inflammatory markers in the development of necrotic enterocolitis is actively studied [8, 25]. Among a large group of potential molecular prognostic factors, a special place is occupied by the system of matrix metalloproteinases, lactoferrin, calprotectin, and fatty acid binding protein. Matrix metalloproteinases are zinc-containing endopeptidases that are synthesized in a latent form and activated by proteolytic cleavage of the amino-terminal domain or conformational changes caused by oxidative stress. Under physiological conditions, the activity of matrix metalloproteinases is stoichiometrically (1:1) regulated by their tissue inhibitors [25, 26, 28,29]. Unfortunately, in the available medical literature, especially in Russian, this issue is practically not covered. Considering the variety of effects of components of the matrix metalloproteinase system and tissue inhibitors in tissues, their study as prognostic factors and the course of necrotic enterocolitis in children is relevant. Calprotectin is a protein containing calcium and zinc ions and has a bacteriostatic and fungicidal effect in vitro. Calprotectin is a non-invasive quantitative direct marker of the activity of the inflammatory process in the intestine in non-specific ulcerative colitis, correlates with the histological and endoscopic picture. This indicator is used to monitor the response to treatment, detect relapses, and prove that the small intestine is involved in the inflammatory process [25, 31]. Fatty acid binding protein is a cytosolic, water-soluble protein released from mature enterocytes of the small and large intestine when the integrity of the cell membrane is compromised. Due to its small size, the protein passes through the glomerular filter and can be detected in the urine in the shortest possible time. In a recent study by researchers from the University of Chicago, the level of this protein was higher in children with necrotizing enterocolitis compared to children without this disease, with a sensitivity of up to 93 %. In addition, the level of fatty acid binding protein was significantly higher in children with perforation of the intestinal wall than in children without perforation [27]. Therefore, this protein can also serve as a prognostic factor in the treatment of necrotizing enterocolitis. Treatment Depending on the stage of the disease, treatment is divided into conservative and operative. In the absence of necrosis and perforation, patients can be treated conservatively. When necrotizing enterocolitis is suspected or proven, the child is removed from feeding and transferred to full parenteral nutrition, a nasogastric tube is installed for decompression [1, 2, 4, 5-7, 9, 12, 13, 17, 18]. Foreign authors mention the use of inflammatory cytokine inhibitors when signs of necrotic enterocolitis appear, while in our country this experience is not available. According to some authors, epithelial growth factor (EGF), heparintherapy, interleukin-10, erythropoietin, and granulocytic acid are used to restore damaged mucosa., colony stimulating factor (G-CSF), also probiotics. A number of animal studies have shown a positive effect with the introduction of immunoglobulin A, L-arginine, nitroglycerin as a source of nitric oxide, pentoxifylline as an inhibitor of tumor necrosis growth factor [2, 32, 33, 35,37,38]. Broad-spectrum antibiotics are a mandatory component of therapy. Preference is given to cephalosporins of the third generation in combination with aminoglycosides. An alternative to them is imipenems with
metronidazole. However, uncontrolled use of antibiotics has shown ineffectiveness of the effectiveness of therapy. Antibiotics should act not only against the bacteria found in necrotizing enterocolitis, but also against the nosocomial flora.[15, 18, 19, 21]. One of the most difficult issues is determining the criteria for performing surgical treatment. Almost all surgeons agree that perforation or necrosis of the intestine serves as an indication for surgery. Ideally, the operation should be performed only after a clear restriction of necrosis zones, but before the development of perforation. At the same time, the diagnosis of intestinal necrosis before the development of perforation is very difficult [2, 7, 15, 17, 19,]. According to foreign authors, the mortality rate remains high and ranges from 18 to 40 % [22], reaching 95-100 % with extensive intestinal necrosis [25]. For the treatment of necrotic enterocolitis in newborns, two methods are most often used: resection of necrotic areas of the intestine with enterostomy or with primary anastomosis [7, 15, 17, 21, 22,35]. There is an active discussion between the proponents of these two methods. Recently, some authors have discussed the issue of primary peritoneal drainage by laparocentesis [2, 15, 19, 22,34]. In 1977, peritoneal drainage was described as a treatment for necrotizing enterocolitis. Ein and its colleagues. Initially, such an operation was proposed to stabilize the condition of patients with a severe course of the disease in order to perform laparotomy in the future. Later, peritoneal drainage was performed as a separate treatment method. Currently, there are no clear criteria for when to perform laparotomy after peritoneal drainage, and when to conduct the patient only on drainage. Analyzing the long-term results of treatment, we can say that the most common complication is short bowel syndrome [26]. Almost every fourth newborn who has had necrotizing enterocolitis suffers from this syndrome. This complication also applies to children who have not undergone surgical treatment. In premature infants who received conservative therapy, despite the normal length of the intestine, the absorption capacity in the areas that were involved in the inflammatory process remains low. In addition, neurological disorders remain the main problem in newborns who survive necrotic enterocolitis. They are manifested by impaired vision, hearing, delayed psychomotor development, etc. Such children have difficulties with adaptation in the social environment [9]. Thus, the treatment of children with necrotizing enterocolitis is a complex problem with a high mortality rate. Many controversial issues concerning pathogenesis, diagnosis, and surgical tactics remain open and need to be resolved.

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