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Possible role of features of the intestinal microbiome in patients with colorectal cancer as a cause of anastomotic leak

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ABSTRACT

Aim. Following the analysis of literature data, to determine significant factors of intestinal obstruction in patients with colorectal cancer.

Materials and methods. We analyzed 84 literature sources from the Scopus, Web of Science, Google Scholar, and PubMed databases, as well as open access articles on Google.

Results. The predominant causes of anastomotic leaks after operations for colorectal cancer are discussed, the role of the microbiome in the development of postoperative complications is analyzed. The intestinal microbiome of patients with colorectal cancer contains bacteria that are not normally found under physiological conditions. These bacteria contribute to the development of disease, suture failure after surgery for intestinal obstruction, and progression of carcinogenesis. This effect is due to the production of bacterial metabolites, the effect on the human immunity, and competition with obligate intestinal microflora. On the other hand, the use of drug therapy, including antibiotics, leads to mass death of obligate bacteria. Therefore, it is important to search for drugs and treatment methods that, if possible, do not have a significant negative impact on the microbiome, but are capable of destroying pathogenic microorganisms. The concept of Russian authors was proposed, which consists in the intraluminal use of rifaximin-α for the prevention of purulent and septic complications and anastomotic leaks during reconstructive surgeries on the distal colon.

Conclusion. Anastomotic leaks after operations for colorectal cancer are largely facilitated by the imbalance of the intestinal microbiome typical of this group of patients, which can be eliminated by the use of antimicrobial drugs.

Keywords: intestinal microbiota, cancer, intestinal obstruction, anastomotic leak

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Возможная роль особенностей кишечного микробиома у пациентов с колоректальным раком как причина несостоятельности анастомоза

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РЕЗЮМЕ

Цель исследования: на основе анализа литературных данных определить значимые факторы кишечной непроходимости у пациентов с колоректальным раком (КРР).

Материалы и методы. Проанализировано 84 литературных источника из баз данных Scopus, Web of Science, Google Scholar, PubMed, а также находящихся в свободном доступе в Google.

Результаты. Обсуждаются преобладающие причины несостоятельности анастомозов после операций по поводу КРР, анализируется роль микробиома в развитии послеоперационных осложнений. Микробиом кишечника больных КРР содержит бактерии, которые в норме не обнаруживаются в физиологических условиях, и сами эти бактерии способствуют развитию заболевания, а также несостоятельности кишечного шва после операции по поводу кишечной непроходимости, прогрессированию процесса канцерогенеза. Этот эффект обусловлен продукцией бактериальных метаболитов, влиянием на иммунную систему человека и конкуренцией с облигатной микрофлорой кишечника. Однако использование медикаментозного лечения, в том числе антибиотиков, приводит к массовой гибели облигатной микрофлоры. Поэтому важен поиск таких препаратов и методов лечения, которые по возможности не оказывают существенного негативного влияния на микробиом, но способны уничтожать патогенные микроорганизмы. Предложена концепция российских авторов, заключающаяся во внутрипросветном применении рифаксимина-α для профилактики гнойно-септических осложнений и несостоятельности анастомозов при реконструктивных операциях на дистальном отделе толстой кишки.

Заключение. Несостоятельности анастомозов после операций по поводу КРР в значительной мере способствуют специфические для этого контингента пациентов нарушения кишечного микробиоценоза, которые могут быть устранены использованием антибактериальных препаратов.

Ключевые слова: микробиота кишечника, рак, кишечная непроходимость, несостоятельность анастомоза

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INTRODUCTION

Currently colon cancer is one of the leading causes of morbidity and mortality in the Russian Federation [1], which reflects the global trend [2]. Colorectal cancer (CRC) affects more than 250,000 people each year and is the cause of about a third of cancer deaths [3].

Genetic predisposition to the disease plays a

certain role in the formation of colorectal cancer, in particular, mutation of the *K-Ras* gene can be accompanied by a constant level of its activity, which allows cells to evade apoptosis and proliferate rapidly and uncontrollably [3]. However, most cases of CRC are sporadic and are largely associated with a combination of manageable environmental risk factors [4].

According to the World Health Organization, risk factors may include race, age, poor family history and genetic predisposition (referring for less than 25% of CRC cases [5]), previous inflammatory diseases of the colon, including familial adenomatous polyposis, adenoma [6, 7].

Intestinal obstruction (IO) in CRC may occur due to the development of the disease (e.g., tumor overgrowth), anticancer therapy (e.g., scarring after radiation therapy), or due to other causes [8]. Usually, IO in such patients leads to severe consequences, and its treatment often presents great difficulties [9].

For many patients with malignant neoplasms of the gastrointestinal tract, dissemination of the abdominal cavity with tumor cells (peritoneal carcinomatosis) is a common route of metastasis and progression of the disease. Despite the encouraging results shown by cytoreductive surgery and intraperitoneal chemotherapy, most patients who develop peritoneal carcinomatosis associated with gastrointestinal cancer have a poor prognosis, and malignant ileus is a common terminal phase of the pathological process [10]. The prognosis in the case of intestinal perforation uncomplicated by carcinomatosis due to IO can also be fatal, especially in the case of fecal peritonitis [11]. There is no doubt that malignant obstruction of the colon is directly associated with cancer recurrence and lower overall survival, regardless of the disease stage and adjuvant chemotherapy [12].

The incidence of anastomotic leaks after surgery for CRC varies, averaging up to 15% of cases. At the same time, the factors leading to this complication are different and can be generalized as patient-related factors (the presence of chronic infections, internal and endocrine diseases) and as surgeon-related factors (the choice of the method of surgical intervention, etc.) [13–18]. According to other data, the incidence is 4–5% [19], 12% [20]. It is known that the risk of anastomotic leaks is higher in male patients than in female patients [21]. However, the factors that correlate with IO in patients with CRC are diverse and remain unclear; the dominant factor has not been determined yet [22].

MATERIALS AND METHODS

We analyzed 84 literature sources from Scopus, Web of Science, Google Scholar, and PubMed databases, as well as open access articles on Google. The analysis of the literature data was carried out taking into account ethical standards developed in accordance with the Declaration of Helsinki of the World Medical Association “Ethical Principles for Medical Research Involving Human Subjects” as amended in 2000 and the Rules of Clinical Practice in the Russian Federation approved by the Order of the Ministry of Healthcare of the Russian Federation No. 266 of 19.06.2003.

RESULTS

Basic approaches to the prevention of IO in patients with CRC. Since the development of anastomotic leaks after bowel surgery for CRC is a life-threatening complication [23], and a failure to properly heal anastomosis can lead to the development of peritonitis, these patients require additional care associated with longer hospital stays and increased costs. High morbidity and mortality rates and a less favorable cancer prognosis are noted in these patients, therefore, the search for optimal biomarkers of anastomotic failure, including microbiological parameters, is extremely important [24]. Especially since surgical trauma seems to cause such complex reactions as genotypic and phenotypic changes in the commensal microbiota, increasing their pathogenic potential, which causes tissue destruction and anastomotic leak [25].

Undoubtedly, adequate medical treatment, including appropriate fluid therapy, early initiation of antibiotics, and treatment of concomitant diseases in accordance with international guidelines, are important for patient recovery after surgery for IO associated with CRC [11].

Experimental and clinical studies have shown that combined perioperative systemic antibiotic prophylaxis and prolonged topical antibiotics against common enteric gram-negative and gram-positive pathogens in intestines after mechanical cleansing

are effective in preventing intestinal anastomotic leaks [26]. All of the above indicates that the search for optimal ways, approaches, and methodological concepts regarding the treatment of such a complex group of CRC patients who were diagnosed with IO is undoubtedly extremely relevant at the present time.

The role of the intestinal microbiota in the development of IO in patients with colorectal cancer. Normal microflora. Recent studies have demonstrated that the gut of patients with CRC contains microbiota that differs from that in the healthy colon, and that this microbiota may contribute to the onset of a malignant disease, intestinal suture failure after surgery for IO, and progression of carcinogenesis [26, 27].

The microbiota consists of various bacterial taxa that inhabit the epithelial barriers of various host organs. Microbiota (microbiome) is a metabolically active ecosystem that interacts with epithelial and stromal cells and plays an important role in human health, performing various functions, such as production of important metabolites, prevention of pathogen infections, and control of overgrowth of certain groups of bacteria to prevent changes in the local environment by toxic bacteria. In addition, microbiota is important for the activation of the host immunity. The number and diversity of microbial species in the intestine increase in the longitudinal direction from the stomach to the colon [28]. Short-chain fatty acids produced by obligate microflora are the main source of butyrate, propionate, and acetate, which are used as an energy source in the intestine and help proliferation and differentiation of intestinal epithelial cells [5].

In the last decade, numerous studies have established a clear relationship between changes in the composition of the gut microbiota and various human pathologies: obesity and associated metabolic disorders (for example, type 2 diabetes and non-alcoholic fatty liver disease), autoimmune diseases (for example, type 1 diabetes and inflammatory bowel disease), and some types of cancer that are characterized by changes in the microbiome and gut [28, 29].

In addition, the microbiota greatly contributes to the development of lymphoid tissue and can modulate the innate and adaptive host immunities. Gut microbiota interacts with elements of a full immune response through dendritic cells or through stimulation of epithelial receptors, even in the absence of bacterial translocation [30].

Based on localization, researchers distinguish between two types of intestinal microbiota: parietal (microbiota of mucous membranes) and luminal microbiota. Currently, luminal microflora is analyzed to a greater extent due to the ease of collecting fecal samples. On the contrary, parietal microbiota is usually examined using intestinal tissue biopsy obtained during endoscopy [31, 32]. Moreover, the composition of the microbiota varies between the epithelial cell layer, the mucus layer, and the lumen [33].

It is the parietal microbiota that is involved in stimulating mucus secretion and production of short-chain fatty acids, such as acetate, butyrate, and propionate, which are considered regulators of intestinal physiology and mediators of the host immunity. Butyrate is involved in colonocyte metabolism, enhances the barrier function of the intestine by increasing the production of mucus and the formation of tight junctions, stimulates the immunity of the mucous membranes, and also has antiinflammatory and antitumor effects, since it inhibits the proliferation of cancer cells [31, 32]. The antitumor effect of butyrate is due to its inhibitory effect on histone deacetylases (HDAC), which promote carcinogenesis. Due to the metabolic shift of cancer cells toward glycolysis, unused butyrate accumulates and inhibits procarcinogenic HDACs. In addition, recent studies show that butyrate can improve the healing of colonic tissue in surgical animal models, especially at the site of reconnection of colon ends, anastomosis, and after surgical resection [32].

Acetate produced by anaerobes, in particular *Bifidobacterium*, is involved in defense mechanisms against external agents, such as enterohemorrhagic Escherichia coli infection [31]. As it was shown in an experiment on rats, after colectomy, the composition of parietal microflora changes with a significant increase in the number of microorganisms of the genera *Enterococcus, Escherichia* and / or *Shigella* in the microbiome. However, it is still unclear to what extent the change in parietal microflora can be reflected in shifts in luminal microflora isolated during a bacteriological examination [31].

Pathological changes in the intestinal microflora in CRC. Dysbiosis is defined as the abnormal and predominant presence of pathogens in the

environment or as alterations in the considered normal proportion of different specimens composing the microbiota. This new ecosystem is also called the pathobiome [30].

A growing body of evidence indicates that disruption of the gut microbiota composition is strongly associated with CRC. Recent studies have identified *Streptococcus bovis*, enterotoxigenic *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Enterococcus faecalis*, *Escherichia coli*, and *Peptostreptococcus anaerobius* as potential initiators of CRC [34, 26].

When the balance of normal microflora is disturbed, the number of intestinal probiotic species of microorganisms belonging to the genera *Bifidobacterium* and *Lactobacillus* decreases, and the number of bacteria producing enterotoxins *Bacteroides, Escherichia coli,* and *Clostridium difficile* increases. Bacteria secrete a variety of toxic factors that damage intestinal epithelial cells, causing a chronic inflammatory response and development of CRC, in particular by activating intestinal mucosal macrophages via M cells. In addition, chronic inflammation under conditions of high levels of oxidative stress leads to a loss of barrier functions of epithelial cells and disruption of humoral and T cell immunity [35].

Changes in the balance of gut bacteria can lead to changes in the levels of gut microorganism metabolites, such as short-chain fatty acids (SCFAs), polyphenols, vitamins, tryptophan catabolites, and polyamines; abnormal levels of SCFAs and molecules associated with amino acid metabolism like polyamines are involved in cancer progression and metastasis in various types of tumors [28]. These microbial metabolites interact with the host immunity and cause release of genotoxic virulence factors. Such microorganisms include *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Enterococcaceae* or *Campylobacter*, *Peptostreptococus*, *Enterococcus faecalis*, *Escherichia coli*, *Shigella*, *Salmonella*, and *Streptococcus gallolyticus* [28, 29, 36]. To date, an excess of *Fusobacterium* in the intestine can be considered a potential biomarker for CRC [29].

Fusobacterium nucleatum is the most frequently observed species in the colorectal tumor microenvironment and affects the progression of the disease through multiple mechanisms [37]. Excess colonization of the intestine by microorganisms of the genus *Fusobacterium* is associated with the activation of macrophages after the activation of certain miRNAs, in particular mRNA-21; miRNA-21 activates interleukin-10 (IL-10) and prostaglandin E2 and causes a decrease in antitumor suppressor functions of T cells. A recent study showed that *Fusobacterium* promotes chemotherapy resistance in CRC by affecting innate immunity receptors TLR4 and MYD88, as well as specific mRNAs (mRNA18a and mRNA4082) responsible for autophagy activation. Thus, patients with high levels of *Fusobacterium* are more susceptible to chemotherapy failure and disease recurrence [29]. The so-called Western diet, characterized by a high intake of sugar and animal fat and low in fiber, is in particular associated with an increase in *Bacteroides* [31]. An increase in *Fusobacterium nucleatum* and *Bacteroides fragilis* is strongly associated with the occurrence of CRC due to inflammatory mechanisms, while *Faecalibacterium prausnitzii* is a protective factor, producing butyrate [38].

A hypothesis has been proposed regarding the relationship between *Fusobacterium nucleatum* and CRC. According to this hypothesis, the proposed pathogenic mechanism involves the activation of the β-catenin signaling pathway that causes cell proliferation (as a consequence of FadA binding with E-cadherin located on intestinal epithelial cells). The observation that *F. nucleatum* is more prevalent in patients with CRC than in healthy individuals is statistically significant. However, the number of *F. nucleatum* and *Bacteroides fragilis* (both in the stool sample and in the tumor tissue) appears to increase along with adenoma to adenocarcinoma progression [30].

Peptostreptococcus spp. is relevant in patients with CRC. A recent study showed that patients with bacteremia caused by *Peptostreptococcus spp.* have an increased risk of CRC. This microorganism produces many saccharolytic and fermented products, including acetic, isobutyric, isovaleric, and isocaproic acids, and may contribute to the acidic and hypoxic tumor microenvironment, which promotes bacterial colonization. However, no major research has been done in this direction to date. As for the procarcinogenic effect, it is known that this microorganism contributes to the accumulation of reactive oxygen species by affecting TLR2 and TLR4 [29, 36].

Peptostreptococcus anaerobius is an anaerobic bacterium that selectively lives in excess in the

colonic lumen and on the mucous membranes of patients with CRC, but its mechanisms of pathogenic and carcinogenic effects remain unidentified. To date, *P. anaerobius* is known to attach to the intestinal mucosa and accelerate the development of CRC in ApcMin /+ mice.

In vitro studies and transmission electron microscopy demonstrate that *P. anaerobius* attaches selectively to CRC cell lines (HT-29 and Caco-2) compared to normal colonic epithelial cells (NCM460) via the *P. anaerobius* cell wall protein, which binds directly to colonic cells via the integrin α2/β1 receptor, often overexpressed in human colorectal tumors and cell lines. The interaction between PCWBR2 and integrin α2/β1 induces active cell proliferation, which also involves the nuclear factor κB (NF-κB) activation pathway, which in turn induces a proinflammatory response as indicated by elevated levels of cytokines, such as IL-10 and interferon-γ, in tumors of ApcMin/+ mice treated with *P. anaerobius*. The identified relationship may be a promising therapeutic target in the management of CRC [39].

Streptococcus gallolyticus (*Streptococcus bovis*) is detected in approximately 20–50% of patients with CRC, while its prevalence in this biotope in the population is no more than 5% [5].

An increase in the enterotoxigenic variant of *Bacteroides fragilis* has been noted in stool samples of patients with CRC; *B. fragilis* degrades the E-cadherin protein and activates nuclear beta-catenin signaling and induces c-Myc expression and cell proliferation [5]. *B. fragilis* toxin activates the Wnt and NF-*k*B signaling pathways and enhances the release of proinflammatory molecules by the epithelium [28]. The presence of enterotoxigenic *B. fragilis* as well as *F. nucleatum* in the colonic mucosa is associated with more advanced CRC associated with elevated levels of inflammatory mediators, including MMP-9 [40].

Bacteroides, especially in combination with *Escherichia coli*, are crucial to the development of CRC (which was confirmed in experiments on mice), including its familial forms. Both the action through the activation of NF-κB and mucin degradation are mentioned among the mechanisms. However, they usually do not exhibit carcinogenic properties independently, outside of associations with other bacteria [29].

E. coli is characterized by the expression of genotoxins, such as cyclomodulins CIF (cycle inhibiting factor), cytotoxic necrotizing factor (CNF-1) or colibactin; in colonocytes, CNF-1 also affects the actin cytoskeleton, causing reversible cellular senescence, which is potentially associated with chromosomal aberrations and genomic instability [29].

Colibactin is another genotoxin of bacterial origin that can interfere with the cell cycle and promote epithelial cell proliferation through DNA damage, mutations, and genomic instability, which is followed by tumor growth [5]. Higher expression of *B. fragilis* toxin and colibactin genes was found in patients with familial adenomatous polyposis compared to healthy individuals. In addition, some microbial metabolites obtained from food can cause genotoxic and cytotoxic effects. *Clostrudium*, *Bacteroides*, and *E. coli* have been reported to have this capacity [30]. Some strains of *E. coli* and *B. fragilis* produce genotoxins [30].

In CRC patients, *Ruminococcus bromii*, *Clostridium clostridioforme*, and *Bifidobacterium longum* have low prevalence compared to normal population [5]. *S. bovis*/*gallolyticus* can colonize and grow in colon tissues through the binding of collagen and histone-like protein A to collagen I, IV, fibronectin, and fibrinogen in colonic tissues [5], and also acts through the activation of NF-κB and IL-8 [29]. *Clostridium difficile* is currently the most common cause of healthcare-associated infections, with an increase in the prevalence, severity, and mortality of nosocomial and community-acquired clostridial infections accounting for approximately one-third of all clostridial infections. There is also an increased incidence of asymptomatic colonization, especially in high-risk patients [41].

The role of Clostridia in this process is evidenced by the studies by individual authors. Pathogenic microflora is responsible for the excess of free radicals, especially *Enterococcus faecalis* [5]. *E. coli* toxin (colibactin toxin) causes cross-links and double-strand breaks in DNA [28]. The virulence of such an aggressive microorganism as *Pseudomonas aeruginosa* is regulated by the presence of specific fermentation products [33].

Possible role of viruses and fungi in the pathological process. The gut microbiome is not limited to bacteria only, but also includes viruses and microscopic fungi. A high viral DNA load is observed in tumors compared to normal benign tissue, which mainly concerns viral infections,

such as human papillomavirus, polyomavirus infections, human herpesviruses [28]. In addition, *Orthobunyavirus*, *Inovirus* and *Tunalikevirus*, *Bacteroides fragilis*, *Fusobacterium nucleatum* and genotoxic *Escherichia coli*, which are involved in the formation of CRC, are also relevant. Moreover, at early and late stages of cancer development, the mechanisms of the influence of microorganisms on the progression of the disease are different [28].

Metabolites of the microbiota. While some bacteria, such as *F. nucleatum*, *E. coli,* or *B. fragilis,* interact directly with the host by binding to receptors on tumor or immune cells, many effects caused by bacteria can be due to secreted metabolites. The gut microbiome is a vast source of secretory proteins and metabolites, constituting a common reservoir of metabolites in the tumor microenvironment [29].

During carcinogenesis, inflammatory cytokines (IL-6 and others) [42] and chemokines produced by cancer cells attract immature myeloid cells and helper T cells involved in inflammation. The pro-oncogenic microenvironment is characterized by the synthesis of growth factors, angiogenic factors, and tissue remodeling enzymes, as well as suppression of the antitumor T cell response, which contribute to tumor progression. In dysbiosis, the permeability of the intestinal wall increases, the cell wall lipopolysaccharides of some bacteria enter the host, which induces the immune system to secrete cytokines and trigger a cascade of reactions that ultimately lead to inflammation. Local inflammation promotes tumor progression through protumorigenic cytokines and chemokines, which act as growth factors and promote angiogenesis [28].

In general, the impact of the altered microbiota is ambiguous. Thus, *F. nucleatum* is associated with a lower level of $CD3^+$ T cells, increased production of TNFα, IL-6, IL-12, and IL-17 (all of which have a prooncogenic effect), which are involved in many immune responses. However, the Fap2 protein produced by this microorganism can prevent the antitumor effect of NK cells and other T cells that bind to inhibitory receptors [30].

In contrast, some microorganisms appear to have a direct protective effect against tumor growth, such as those that produce short-chain fatty acids (butyrate or acetate). According to previously published data, *Bifidobacterium* appears to be able to inhibit tumor progression by reducing infection by enteropathic microorganisms and reducing the production of bile products. Moreover, some microbes may exhibit antitumor activity through interactions with the immune system. This positive effect is associated with stimulation of phagocytes, increased NK cytotoxicity, and increased production of immunoglobulins, including IgA (which promotes mucosal barrier activity). Data from experimental studies show that *Bifidobacterium* can also contribute to the antitumor immune response by inhibiting the NF-κB signaling pathway. Similarly, *Faecalibacterium prausnitzii* may have a positive effect by inducing IL-10 secretion and modulating Treg response. IL-10 can control the proliferation of Th17 cells, stopping the progression of cancer. In addition, IL-10 suppresses TNFα production and iNOS expression [30].

CRC is usually treated with cytotoxic agents, such as 5-fluorouracil, capecitabine, and oxaliplatin, which interfere with DNA replication. Platinum-based anticancer drugs, such as oxaliplatin, cause severe toxicity to many organ systems, including the intestine. Its toxicity also affects the gut microbiome as it damages rapidly regenerating intestinal mucosal cells, disrupts immunological barriers, and alters environmental cytokines and inflammatory markers. High levels of *F. nucleatum* have been shown to promote chemoresistance in CRC, as *F. nucleatum* attaches to host epithelial E-cadherin, promoting colorectal carcinogenesis through Fusobacterium adhesion. *F. nucleatum* has also been found to mediate chemoresistance through targeting specific miRNAs and autophagy elements. Its direct association with CRC recurrence has even been proposed as a method for predicting patient outcomes or changing chemotherapy regimens [40].

Thus, CRC is characterized by altered production of bacterial metabolites directly involved in cancer metabolism. New evidence suggests that a high-fiber diet with polyunsaturated fatty acids, polyphenols, and probiotics, known to regulate the gut microbiota, may not only be a potential mechanism to reduce a CRC risk in primary prevention, but also contribute to an enhanced response to cancer therapy when used as an adjuvant to conventional treatment of the disease [28].

The gut microbiota composition altered in the postoperative period can lead to serious complications, including anastomotic failure and surgical site infections. In addition, intestinal microbiota can be used as a possible biomarker

in predicting long-term outcomes after surgical treatment for CRC [43].

Thus, the gut microbiota of patients after colorectal surgery changes due to surgical stress. The development of complications after colon surgery for CRC (including anastomotic failure and surgical site infections) may depend on bacterial shifts, which may also affect the prognosis and survival in patients with postoperative CRC [43].

Evidence has been accumulated for 60 years that anastomotic failure is caused by pathogens, classic examples of which are *E. faecalis* and *P. aeruginosa*, which have the ability to degrade collagen and / or host matrix metalloproteinase-9 (MMP-9) [26]. Specific bacterial infections increase the risk of anastomotic failure. In particular, *Pseudomonas aeruginosa* and *Enterococcus faecalis* (as bacteria that strongly affect collagen) have been shown to play a role in this process, while locally administered antibiotics turned out to be more effective [24].

Anastomotic leaks, which are a very serious problem [44], are currently associated with *Enterococcus faecalis*, since this pathogen has high collagenase activity and activates MMP-9, which are the main contributors to tissue destruction and intestinal inflammation. MMPs are a group of proteolytic enzymes that mediate the degradation of the extracellular matrix and regulate the release of growth factors, chemokines, and adhesion proteins. High levels of MMP-9 and MMP gelatinase with type IV collagen as the main substrate have been shown to be a marker of invasion and worsen cancer outcome in patients with CRC. The fact that strains of *E. faecalis* appear to play an important role in the pathogenesis of anastomotic leaks and remain in anastomotic tissues despite current bowel preparation before surgery suggests that microbiome suppression and the presence of a microbiome may be overlooked elements playing a role in local recurrence. These collagenase-producing *E. faecalis* strains can also interact with resident macrophages [40, 30]. Anastomotic leaks in CRC are associated not only with *Enterococcus* spp., producing beta-lactamase, but also with *Escherichia* spp. as the most common pathogens [45].

Collagenase-producing families Bacteroidaceae, Lachnospiraceae [46], and *Clostridium difficile* [41, 30] are also important for intestinal anastomotic failure. It was found that high abundance of *Bacteroides fragilis* is associated with a worse prognosis, while low abundance of *Prevotella*, *Bacteroides,* and *Faecalibacterium prausnitzii* seems to be a more favorable prognostic factor [47].

Impact of colorectal surgery on the gut microbiota. To date, the impact of colorectal surgery on the gut microbiota has not been fully clarified [43]. Undoubtedly, the use of isotonic laxatives (e.g., polyethylene glycol) as a preoperative preparation adversely affects the microbiota. At the same time, under favorable circumstances, in non-oncological patients who received such preoperative preparation, the parameters of the intestinal microbiota approach the normal range on average by day 14 after surgery [43]. It has been established that patients with CRC have an increased number of *E. coli* and *Staphylococcus* in the postoperative period [43].

Perioperative medications can also change the microbiome composition. Antacids neutralize gastric secretion, which can disturb the balance of acid-sensitive organisms in the intestine. Vasoactive drugs, which are often used in critically ill patients, can cause intestinal hypoxia affecting bacterial virulence. Opioids impair gastrointestinal peristalsis and motility, thereby reducing mechanical removal of excess bacteria from the lumen. This can lead to intestinal obstruction, dysbiosis, and / or bacterial overgrowth.

Perioperative interventions may cause increased multiplication of virulent bacterial strains (e.g., *Enterococcus*, *Pseudomonas*) capable of transforming into strains with a more aggressive tissue-destroying phenotype. These changes may contribute to the development of anastomotic leaks [33]. Instead of aggressive preoperative preparation with saline laxatives and broad-spectrum antibiotics, gentle bowel cleansing with nutritional supplements and non-microbicidal antivirulence agents is currently considered, which does not lead to mass destruction of the microbiome that is common nowadays. A successful practice is manifested by a decrease in the number of Enterobacteriaceae bacteria in this group of patients [40]. Carbohydrate food additives that suppress the virulence of *P. aeruginosa*, *E. faecalis,* and *Serratia marcescens* without affecting their growth are also considered [40].

However, one of the modern reviews conducted in accordance with the Oxford Center for Evidence-Based Medicine guidelines and principles (databases

used included PubMed, Cochrane Library, Embase, Scopus, and Google Scholar), summarizing published data on the prevention of anastomotic leaks after colorectal surgery, argued that mechanical bowel preparation does not reduce the risk of anastomotic failure, as well as the choice of surgical approach and strategy, excluding low ligation of the inferior mesenteric artery; while the use of an oral antibiotic reduces the incidence of anastomotic leaks [48].

Some authors recommend the use of postoperative antibiotics affecting *Escherichia coli* and *Enterococci* as the most common pathogens [49, 50]. At the same time, some modern authors suggest using antibiotics, such as gentamicin in combination with erythromycin, as preoperative preparation [20].

Recent studies by foreign authors provide data on the comparative efficiency of various oral antibiotics, including both selective and broad-spectrum ones. Selective antibiotics are known to target only certain (aerobic, Gram-negative) bacteria, while local anaerobic bacteria are mostly not affected. The disadvantage of broad-spectrum antibiotics is that they lead to more extensive destruction of bacteria, which can lead to microbial dysbiosis [51].

The following regimens are given: kanamycin and metronidazole orally with a short course of parenteral cefmetazole, kanamycin with erythromycin orally and parenteral cefotiam for 48 hours, kanamycin with erythromycin orally and cefmetazole administered parenterally, polymyxin B with tobramycin and amphotercin B orally and cefuroxime intravenously, etc. [51].

Many authors prefer topical (oral or intraluminal) use of antibiotics in this case [52, 53]. Russian authors report the successful intraluminal use of Alfa Normix® suspension (rifaximin-α) for the prevention of purulent – septic complications and anastomotic failure during reconstructive surgery in the distal colon [54].

CONCLUSION

Today the role of the pathobiome in the formation of IO and suture failure during anastomosis is undeniable, along with the fact that the use of antibiotics can disrupt the endogenous microbiome and cause resistance of pathogens to antibiotics. Therefore, it is important to search for such drugs and treatments that, if possible, do not have a significant negative effect on the microbiome, but are able to destroy pathogenic microorganisms [25] and, thereby, prevent intestinal suture failure and cancer progression.

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Kosareva P.V., Konev R.A. – conception and design, analysis and interpretation of the data. Godovalov A.P. – conception and design, justification of the manuscript. Sivakova L.V. – critical revision of the manuscript for important intellectual content. Samodelkin E.I. – final approval of the manuscript for publication.

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