Intestinal microbiota and pancreatic diseases

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Infectious concept is a permanent magnet.

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Diseases of the pancreas (pancreas) are gaining increasing medical and social importance both in terms of the complexity of diagnosis and treatment, their cost, and the temporary and permanent disability of patients, reducing their life expectancy. Among the factors of etiology and pathogenesis of pancreatic pathology in recent years, intestinal microbiota has been of increasing interest [87].

Intestinal microbiota in acute pancreatitis (AP)

A systematic review was performed that revealed the potential role of the microbiota of the digestive tract in the development of pancreatic pathology [60]. It included only one study of intestinal microbiota in AP [85]. This multicenter study included 108 patients (44 severe AP, 32 light AP, and 32 healthy). There was no significant difference in the total number of fecal bacteria in the three groups. However, the populations of Enterobacteriaceae and Enterococcus were larger in all patients with AP compared to healthy ones. There was no difference between groups with severe and mild AP. The amount of Bifidobacterium was lower in all patients with AP compared to healthy ones. In severe AP, the level of endotoxin and cytokines in the blood was higher than in mild AP and in healthy ones.

The latest revision of the Atlanta international classification distinguishes two stages of AP [19]: the initial stage (the first 14 days), when there is a risk of developing a systemic inflammatory response syndrome (CVD) and organ failure in the absence of bacterial infection, and the late stage (usually after two weeks with the onset of symptoms), when persistent systemic inflammation is combined with bacterial infections or local complications [52].

Bacterial complications, such as infection of pancreatic fluid reservoirs, as well as the presence of CVD and multi-organ dysfunction (MODS), are factors that are associated with a high risk of patient death [92]. The risk of death in infected pancreatic necrosis is approximately 30% [20], but it is higher in patients who have colonization of the intestine with gram-negative bacteria [16]. Insufficiency of intestinal barrier function due to increased intestinal permeability plays a key role in the occurrence of septic complications of AP; this occurs mainly as a result of a violation of microcirculation in the intestinal wall, which leads to intestinal ischemia and its reperfusion damage with the release of free oxygen radicals [24]. In an increase in intestinal permeability, not only damage to enterocytes matters; systemic oxidative stress leads to impaired function of the mucosa covering enterocytes from bacterial damage [36]. Moreover, bacterial translocation not only leads to infection of necrosis sites, but can also cause non-infectious pancreatic inflammation due to activation of acinar cell enzymes through stimulation of the cytosolic protein NOD1 and subsequent production of inflammatory mediators [90].

A meta-analysis of 18 prospective clinical trials showed that three out of five patients with severe acute pancreatitis develop intestinal barrier dysfunction [96]. Some studies have shown higher intestinal permeability in severe AP compared with mild forms [16, 51, 70]. M.G. Besselink et al. examined 731 patients with AP and found that bacteremia (in most cases, coming from the intestines) was significantly associated with high mortality [21].

R. Senocak et al. investigated the role of colon bacteria in AP. They compared rats that underwent and did not undergo total colectomy in which experimental AP was induced. Colectomy, which led to an overgrowth of the microflora of the small intestine (the syndrome of

overgrowth of bacteria — BOS), increased the likelihood of pancreatic infection due to bacterial translocation [81].

I.D. Van Felius et al. investigated the effect of necrotic AP on BOS, translocation of bacteria, and pancreatic necrosis infection in experimental animals. Excessive growth of gram-positive cocci, gram-negative and anaerobic microorganisms in the duodenum of animals with necrotic AP was revealed in comparison with the control group without AP. There was a positive correlation between the severity of pancreatitis and BOS in the duodenum [91]. These data from preclinical studies are somewhat consistent with a small number of clinical studies conducted in patients with AP.

There are significant results of preclinical and clinical studies confirming the key role of intestinal barrier dysfunction, bacterial translocation and endotoxemia as an additional factor in the development of CVD, MODS and the risk of infection in necrotic AP [52]. Alcohol consumption can contribute to the mechanisms of BOS progression and intestinal permeability disorders, which leads to an excess of endotoxin in the bloodstream [46]. From this point of view, the hypothesis is substantiated that treatment strategies that focus on restoring the barrier function of the intestine and its decontamination during AP, especially at its initial stages, could lead to a reduction in the infection of pancreatic necrosis and mortality. Appropriate infusion therapy for AP is associated with a better prognosis because it supports intravascular volume and reduces the likelihood of intestinal wall ischemia [94]. Enteral nutrition in the initial stage of AP, when the prognosis of a severe course takes place, can favorably affect the maintenance of the structural integrity of the mucous membrane and reduce the translocation of bacteria from the intestine with a decrease in mortality, MODS, and CVD [71, 86], as shown in the meta-analysis. which compares enteral nutrition with total parenteral nutrition [15]. While appropriate infusion therapy and enteral nutrition in the early stages are accepted treatment strategies for severe AP, the use of probiotics, which might seem simple and safe for decontamination of BOS, correction of intestinal barrier insufficiency, has been associated with negative consequences and is currently not recommended (see below). However, in vitro studies have shown that probiotics help reduce both the likelihood of bacterial translocation and the severity of AP [14, 64]. Their effectiveness in reducing the incidence of infectious complications and in improving the overall clinical results in patients with AP has also been confirmed by small in vivo clinical trials using Saccharomyces boulardii and strains of other bacteria [67, 75]. A larger, multicenter, double-blind, randomized trial called Probiotics in Pancreatitis Trial (PROPATRIA), "Probiotics for the Study of Pancreatitis," was conducted in 150 patients with predicted severe AP who were given probiotic or placebo for 72 hours from the onset of the disease [21]. Patients of the main group were prescribed a multivariable probiotic mixture, which included approximately equal amounts of two different types of Bifidobacterium, three different types of Lactobacillus, one type of Lactococcus with a total daily dose of 1010 CFU. The study showed a higher mortality rate in the group treated with probiotics, mainly due to mesenteric ischemia. In patients with severe AP, an increase in intestinal permeability and MODS was observed. The authors concluded that the side effects of probiotics were associated with increased intestinal permeability in severe AP, which could be aggravated by using a very large dose of the probiotic mixture [21].

Some authors suggested that the negative results of the PROPATRIA study could be due to the large amount of fermentable carbohydrates in the patients 'diet, as well as the wrong dose and the late use of probiotics [23]. A more thorough study should focus on this topic using special strains and doses of probiotics. In a recent systematic review and meta-analysis of clinical trials on the use of probiotics in AP, including the PROPATRIA program, neither a positive nor a negative total effect of probiotics on the course of AP was revealed. The heterogeneity of studies with respect to the types and strains of probiotics, their concentration and duration of treatment is obvious [40].

Intestinal microbiota in autoimmune pancreatitis (AIP)

A possible role of intestinal microbiota in the pathogenesis of AIP. A hypothesis has been proposed that intestinal bacteria participate in pathogenesis, since in an animal experiment,

exposure to avirulent bacteria, such as Escherichia coli after heating, causes damage to the pancreas of the AIP type due to dysregulation of the genetically determined immune system [45]. Symbiotic bacteria, which are usually harmless, can, under certain circumstances, such as features of the major histocompatibility complex (MHC), activate the pathogen-associated molecular structure (PAMP) or non-pathogenic microorganisms associated with molecular structures (MAMPs) that determine progression in AIPs, possibly using a molecule-antigen antigen with the development of a specific autoantigenic T-cell and antibody production [44].

Helicobacter pylori (Hp) is involved in the pathogenesis of AIP via molecular mimicry [87]. Homology was proved between Hp α-carbonic anhydrase and pancreatic carbonic anhydrase II [42], as well as between the plasminogen binding protein Hp and the human n-recognizing ubiquitin-protein component of E3 ligase receptor 2 (UBR2) [54]. These proteins, respectively, are present in the ductal and acinar cells of the pancreas. In addition, homologous segments of Hp α-carbonic anhydrase include the HLA component, which is associated with a high risk of developing AIP [48]. Further research is needed on the role of microbiota, in particular Hp, in the pathogenesis and development of AIP [52].

Intestinal microbiota in chronic pancreatitis (CP)

CP treatment is a difficult problem for a doctor. In this treatment, one of the important goals is to compensate for exocrine pancreatic insufficiency (IR). A frequent factor hindering the achievement of this goal is BOS [5, 26, 33]. It is this, first of all, that causes interest in the causes, pathogenesis, consequences, and treatment of BOS in CP [68, 69].

What is the frequency of BOS in CP? According to various authors, it ranges from 0% to 92% [30, 41, 57].

In a case-control study, which included 43 patients with CP (without previous surgical treatment) and 43 who were practically healthy, BOS was diagnosed using a hydrogen test with glucose. It was found that in CP, the frequency of BOS is 21%, and in the control — 14% (p=0.57) [84]. Perhaps this result is associated with an insufficient number of patients. It is noteworthy that the authors found a connection between the presence of BOS in patients with CP and reduced levels of vitamin D in the blood, which is probably due to microbial deconjugation of bile acids and more pronounced malabsorption of fat in BOS. In addition, an increased level of blood folate was observed in patients with CP and BOS than in those without CP. This is probably due to bacterial fermentation of the substrate in the lumen of the small intestine with corresponding increased folate production. This phenomenon was previously described at BOS [41].

It is interesting that Yu.Ya. Kotsaba et al. (2016) found in BOS in patients with CP a deficiency of vitamins B1 and B6 [5].

In another prospective, single-case, case-control study, 31 patients with CP and 40 healthy subjects who underwent a hydrogen breath test with lactulose were examined. The frequency of BOS in CP was significantly higher (37.8%) than in the control (2.5%; p <0.01). Interestingly, BOS was significantly more frequently detected in women with CP than in men (66.6% and 27.3%, respectively, p <0.01) [88].

In our study, the diagnosis of BOS was carried out in 33 patients with CP and 30 healthy ones by bacteriological examination of aspirate from the initial sections of the jejunum. In patients with CP, the microbial flora in the ejunal contents was detected more often (66.7%) than in healthy ones (13.3%; p <0.001). The average number of microorganisms in the secretory chyme from the small intestine in the examined patients was also increased to $162.6 \times 10^3 \pm 32.1 \times 10^3$/ml (in healthy patients this indicator was 160.0 ± 21.0/ml; p <0.001). The number of species of microorganisms in the contents of the small intestine significantly differed (p <0.05) from the control group. So, with CP, the number of bacterial species reached 1.03 ± 0.17, and in healthy ones — 0.14 ± 0.09. In addition, it is important that only one type of microorganism, Enterococcus, was revealed in healthy individuals in the small intestine contents, and in patients with CP one type of microorganism was detected only in 45.5% of cases. With a frequency of 9.1%, 2 species were determined, and with a frequency of 12.1%, 3 species of microorganisms [43].

We analyzed the frequency of detection of various types of bacteria in the small intestine with CP: in 39.4±8.5% — E. coli, in 21.2±7.1% — staphylococci, including 6.1±4, 1% — hemolysing staphylococci, enterococci were detected in 15.2±6.2% of cases, B. faecalis alcaligenes in 3.0±2.9%, and paracane bacilli in 3.0±2.9%. In 18.2±6.7% of cases in patients with CP in the small intestine contents, yeast and yeast-like fungi were found [43].

In another study, we conducted a hydrogen breath test with lactulose in 124 patients with CP and diagnosed BOS in 80% of patients with biliary CP and in 92.5% of patients with alcoholic CP [12].

H.M. Ní Chonchubhair et al. performed a hydrogen breath test with glucose for 35 patients with CP. It has been shown that the incidence of BOS in CP is 15%, and it is significantly higher in cases of permanent residence, diabetes mellitus, alcohol abuse, and proton pump inhibitors [65].

Interesting results were obtained in a study by F. Frost et al. The authors examined 1795 healthy volunteers who did not have symptoms of pancreatic diseases. A polymerase chain reaction was performed to identify microorganisms in the feces, a fecal elastase test, and a secretin test to evaluate pancreatic function. The decrease in fecal elastase-1 was strongly negatively correlated with the diversity of intestinal microorganisms. This correlation was more pronounced than the relationship of diversity with age, body mass index, gender, smoking, alcohol consumption, and dietary features. Significant changes in the number of 30 taxa were noted, such as an increase in Prevotella and a decrease in Bacteroides, which indicated a shift from the first enterotype to the second. The change in the results of the secretin test also correlated with changes in the microbiota, but to a lesser extent [38].

In 2016, the results of a meta-analysis were published, which included 9 randomized trials (336 patients with CP) [25]. Studies were selected in which BOS was diagnosed using hydrogen breath tests (with glucose, galactose, sucrose or xylose) and/or bacteriological examination of aspirate from the small intestine. These were case-control studies or cross-sectional studies. The incidence of BOS for CP was 36% (95% confidence interval 17–60%). The relative risk of BOS for CP compared with the control was 4.1 (95% confidence interval 1.6–10.4). The higher incidence of BOS for CP was determined in those studies that included both operated and non-operated patients, compared to studies that included only non-operated patients. The authors noted a higher frequency of diagnosis of BOS when using the breath test with lactulose than with glucose and other substrates (it should be noted that the breath test with lactulose can give false positive results [10]). It is crucial that treatment with BOS for CP with rifaximin, like treatment with BOS due to other diseases, was associated with a decrease in the severity of malabsorption and symptoms of pancreatitis [82].

According to the results of the meta-analysis of 2017, quantitative and qualitative changes in the composition of the intestinal microbiome are characteristic of CP patients: a decrease in the number of Bifidobacterium and Lactobacillus and an increase in the number of Enterobacteriaceae. The presence of concomitant diseases affected the composition of the microbiota: in patients without diabetes, the number of Bacteroidetes decreased, and the number of Bifidobacteria increased in the absence of permanent residence permit. It is important that the treatment of BOS with CP rifaximin (Alpha Normix) was associated with a decrease in the severity of malabsorption and pancreatitis symptoms [60].

Several mechanisms are important in the pathogenesis of BOS with permanent residence permit. In patients, gastrointestinal motility changes (both due to permanent residence permit and when using opiates; in some cases, impaired motility is due to diabetic gastroparesis) and biliopancreatic secretion in the digestive period. In patients with CP, the parallelism between inter-digestive motility and pancreatic secretion is impaired. Given that this secretion is reduced, such violations can contribute to the development of BOS [3, 33, 72]. The appointment of proton pump inhibitors that suppress gastric secretion is also favorable [8, 55].

Under a permanent residence permit, undigested nutrients entering the small intestine undergo rotting and fermentation, creating a breeding ground for bacteria in the form of insufficiently hydrolyzed chyme components. Against the background of these processes, due to the

accumulation of gaseous waste products of bacteria in the duodenum, duodenal hypertension forms, and the evacuation of chyme slows down. Duodenal hypertension leads to a violation of the outflow of bile and pancreatic secretion, which exacerbates pancreatitis, reduces the degree of emulsification of fats and enhances steatorrhea [1].

All this occurs against the background of violation of local immunity and secretory IgA production [66]. In the case of biliary pancreatitis, deficiency of bile acids with antimicrobial activity and also a decrease in the pool of free fatty acids formed during lipid hydrolysis and also having bactericidal function are also important [1].

BOS helps to stimulate local immunity, the penetration of serum Ig into the intestinal lumen to ensure contact between antigens and antibodies at the site of their penetration. The increased permeability of the intestinal wall is the reason for the absorption of insufficiently hydrolyzed macromolecules. This is the background for the formation of immediate hypersensitivity to food allergens [4]. In addition, lipopolysaccharide (endotoxin) is a component of the outer membrane of most gram-negative bacteria, being absorbed into the bloodstream, causes intoxication, aggravates inflammation of the pancreatic parenchyma and is involved in the pathogenesis of steatohepatitis [3, 43].

We have already discussed not only the pathogenesis of BOS with permanent residence permit, but also the negative effect of BOS on the pancreas and its exocrine function. We also note some important mechanisms of the "reverse side of the coin", when the BOS formed as a result of a residence permit aggravates digestive disorders.

The ingestion of residues of insufficiently digested food into the colon due to a deficiency of pancreatic enzymes stimulates the proliferation of the bacterial flora in it, due to which they split (progression of dysbiosis of the colon) with the possible subsequent retrograde penetration of the corresponding bacterial flora into the small intestine, normally containing a small amount microorganisms through the bauginium damper. An increase in pressure in the colon cavity due to the accumulation of gaseous cleavage products of insufficiently assimilated food in it contributes to the formation of cecoileal reflux [2, 6].

These gases (indole, skatol, phenol, cresol, hydrogen sulfide, carbon dioxide, hydrogen, ammonia, etc.) and bacterial endotoxins can increase intestinal peristaltic activity with accelerated passage of food through it, which reduces the time of contact of pancreatic enzymes with food substances in the cavity and membrane digestion, enhances diarrhea. As a result, the digestion of the chyme components is deteriorating (enterogenic pancreatic insufficiency). The products of bacterial breakdown of food in the intestine can lead to organic changes in its mucous membrane (dystrophy, inflammation), as a result of which absorption of the final breakdown products of food substances under the influence of pancreatic enzymes and the small intestine may deteriorate. Deconjugated bile acids, which are formed in excess during bacterial contamination of the initial sections of the small intestine, also contribute to this, which have a damaging effect on its mucous membrane [2, 6, 11].

Another most important aspect of BOS in CP is a decrease in the effectiveness of enzyme preparations against the background of microbial colonization of the small intestine, as we indicated above. Low pH in the duodenal lumen leads to inactivation of endogenous as well as exogenous lipase if it is taken by the patient as part of an envelope-free enzyme preparation. In addition, acidification of the duodenal lumen prevents the release of lipase from enteric-coated enzyme preparations in the proximal small intestine, leads to the precipitation of bile acids, their premature microbial deconjugation and absorption. As a result, the pool of bile acids involved in the emulsification of fats is reduced. A decrease in pH in the lumen of the small intestine also leads to inactivation of enterokinase, which also contributes to the formation of maldigestion [3, 7, 33].

It has already been indicated above that, according to a meta-analysis, rifaximin is effective in the treatment of BOS with CP. The same results were obtained by E. Trespi et al. (1999). They performed a hydrogen breath test with glucose for 35 patients with CP and revealed BOS in 34% of cases. Rifaximin 400 mg 3 times a day for 7 days was prescribed to these patients. The

treatment courses were repeated for 3 consecutive months. Treatment with BOS was effective in all cases and helped to reduce the severity of malabsorption [89].

The efficacy and safety of rifaximin (Alpha Normix) with BOS has been confirmed in a number of evidence-based studies and in other diseases (including irritable bowel syndrome (IBS)) in children [78] and adults [32, 50, 73, 77].

We give an example of the effective elimination of BOS according to the results of a double-blind randomized controlled trial by M. Di Stefano et al. (2000) [32]. 26 patients with BOS diagnosed with a glucose hydrogen breath test were examined. Patients were divided into 2 groups: those who received rifaximin 400 mg 3 times a day for 7 days and those who received chlortetracycline 333 mg 3 times a day for 7 days. The results are presented in Fig. 1. A positive breath test, i.e. the presence of BOS, after treatment was significantly less likely to occur in the rifaximin group (27%) than in the chlortetracycline group (70%; p <0.01). Rifaximin also significantly reduced the severity of clinical manifestations (diarrhea, flatulence, etc.), which was not observed in the chlortetracycline group.
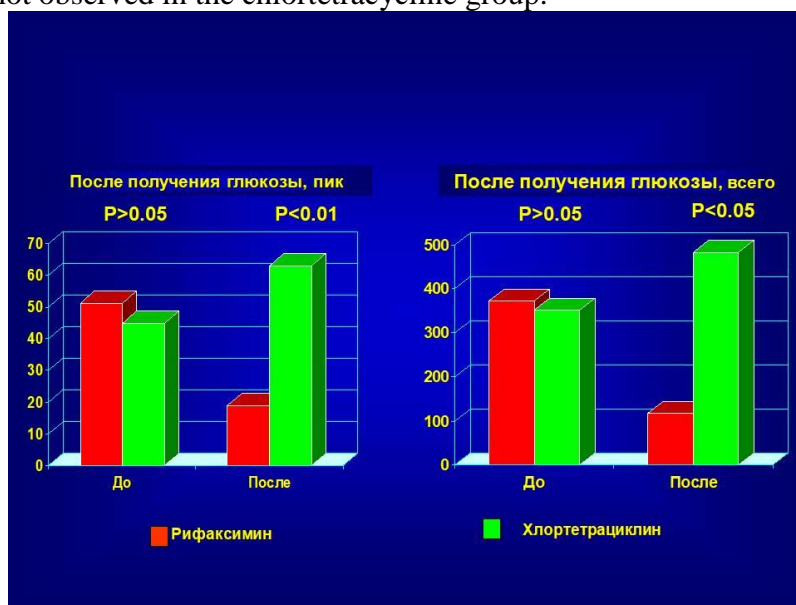
Fig. 1. Isolation of H2 in exhaled air during a breath test with glucose (pm/min) before and after treatment (M. Di Stefano et al. (2000) [32])

It is proved that rifaximin in 87% of cases eliminates BOS caused by the use of proton pump inhibitors [55], which is especially important for CP.

P. Meyrat et al. (2012) examined 106 patients with IBS with diarrhea and BOS (performed a hydrogen breath test with lactulose) [61]. Patients received rifaximin 200 mg 4 times a day for 14 days. The results are presented in Fig. 2. It is important that the improvement lasted at least 3 months after treatment.
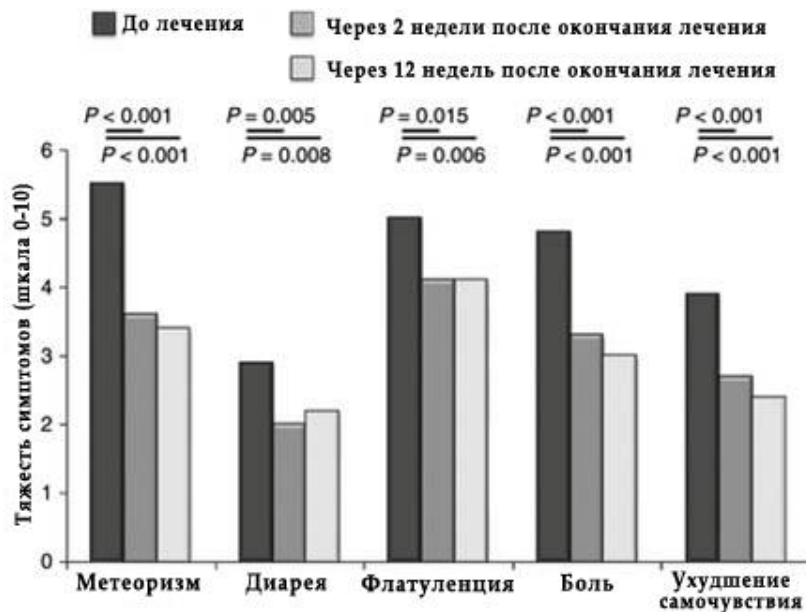
Fig. 2. The dynamics of symptoms of IBS with BOS under the influence of rifaximin treatment (P. Meyrat et al. (2012) [61])

Following advantages of Alpha Normix (rifaximin) should be emphasized [79]:
– has a bactericidal effect — inhibits the synthesis of bacterial RNA, because irreversibly binds to bacterial DNA-dependent RNA polymerase;
– wide antibacterial spectrum of action — the majority of Gr + and Gr-bacteria, both aerobic and anaerobic;
– practically not absorbed into the blood when taken orally (<1%), reaches a high concentration in the mucous membrane of the digestive tract (> 8.0 μg/g);
– concentration of rifaximin in the blood is negligible even in the treatment of patients with damage to the intestinal mucosa (with shigellosis and ulcerative colitis);
– excellent safety profile due to low absorption in the intestine;
– for 6 years, the FDA recorded only 9 complaints about adverse reactions, and only 3 were identified as serious;
– selective action only in the lumen of the intestine;
– since rifaximin is not absorbed, its use does not lead to the development of resistant strains in other organs (for example, in the lungs);
– resistance to rifaximin is formed in chromosomal genes and, accordingly, is not transmitted to other bacteria, resistant strains are unstable and unable to colonize the digestive tract;
– high concentration of rifaximin in the intestine prevents the development of resistant strains;
– resistant strains are rapidly excreted from the intestine after discontinuation of treatment.

Rifaximin has other (other than antimicrobial) potential mechanisms of action [73]. In a study of cytokine profiles in IBS, J. Cheng et al. (2012) found that rifaximin can reduce the expression of pro-inflammatory cytokines (e.g. tumor necrosis factor-α) by binding to the pregnan-X receptor [29].

Rifaximin can also affect the function of intestinal bacteria by altering bacterial mucosal adhesion, bacterial metabolism, or virulence. Rifaximin is able to suppress the interaction of bacteria with a macroorganism and the activation of the immune response [73].

Alpha Normix not only acts selectively on the pathogenic flora, but also modulates the microbiota, i.e. after its application, the growth of beneficial (bifido-, lacto-) bacteria also increases, i.e. in fact, it works as an eubiotic [74, 98].

In a study of the effects of rifaximin on the final products of bacterial metabolism, the administration of a drug at a dose of 550 mg 2 times a day led to an increase in the levels of saturated and unsaturated fatty acids, as well as products of carbohydrate metabolism. Changes

in the metabolic function of bacteria can have a beneficial effect on various symptoms of diseases of the digestive tract [18].

The likely mechanism of action of rifaximin is thought to be the effect on intestinal motility [73].

In the development of BOS with CP, alcohol abuse is important, as mentioned above. A. Vonlaufen et al. reviewed the role of alcohol in increasing intestinal permeability and concluded both its direct toxic effect on the intestinal mucosa and indirect effect through the bacterial metabolism of ethanol into acetaldehyde followed by damage to epithelial bonds [93]. This leads to an increase in the level of serum endotoxin emanating from bacteria, in correlation with pancreatic fibrosis and multiple organ failure. In this scenario, bacterial endotoxin lipopolysaccharide is an aggravating CP factor.

Intestinal microbiota in pancreatic cancer

A better understanding of risk factors and potential options for pancreatic cancer prevention could potentially open up opportunities for improving the epidemiological parameters of this almost fatal disease. The main risk factors for pancreatic cancer are currently considered tobacco smoking, alcohol abuse, diabetes mellitus, obesity and CP [53, 87]. What do all these risk factors have in common? This is their pro-inflammatory activity. It is important that in animals with experimental pancreatic cancer, it was shown that inflammation can activate carcinogenic pathways, mainly through KRAS and NF-kB with their effectors [99]. There are close relationships between the immune system and microbiota; their stability is crucial for the normal state of the immune system [80]. Dysbiosis is associated with chronic activation of innate immunity and, in turn, with chronic inflammation in many diseases [31, 63].

Recognition of microbiotic profiles by toll-like receptors (TLRs) is a powerful pro-inflammatory stimulus, and binding of MAMPs to these receptors promotes the development of cancerous tumors. In this context, it has been hypothesized that the symbiotic intestinal microbiota may play a role in the development of a "pro-inflammatory" state, and therefore, favors pancreatic carcinogenesis. It is noteworthy that changes in the intestinal microbiota are associated with other diseases that are per se risk factors for pancreatic cancer, for example, diabetes and obesity. Type 2 diabetes has been proven to be associated with intestinal dysbiosis [49].

Evidence has been accumulated confirming the relationship between intestinal microbiota and obesity [52]. Lower levels of Bacteroidetes in obese patients compared with control groups are one example of the many variations found with an increased body mass index [17, 83].

However, more specific relationships between intestinal microbiota and pancreatic cancer have not yet been investigated. Interesting data reflect the relationship between oral microbiota and pancreatic cancer. Studies have been conducted to elucidate the relationship of certain bacteria, for example, involved in the occurrence of periodontitis, with pancreatic cancer. The validity of these studies is related to previous data on the increased risk of many tumors, such as cancer of the oral cavity and gastrointestinal tract in patients with periodontitis, while cancer of the lungs, prostate, blood and other types of cancer are associated with it to a lesser extent [37]. In a prospective study D.S. Michaud et al. examined a group of men — medical workers — and observed them for 16 years. Throughout the study, 216 new cases of pancreatic cancer were diagnosed. After analyzing the relationship with age, tobacco smoking, diabetes mellitus and body mass index, it turned out that men with periodontitis had an increased risk of pancreatic cancer compared to those in which periodontitis was not detected (RR=1.64, 95% CI: 1, 19 to 2.26). Moreover, in those who never smoked, but suffered from periodontitis, the risk of pancreatic cancer was doubled, which excludes the possibility that the relationship was distorted by the smoking factor [62].

The relationship between periodontitis and pancreatic cancer risk has been confirmed by other studies [27], as well as a meta-analysis [58]. The biological mechanisms of the relationship between periodontitis and pancreatic cancer are a promising field for research. Since periodontitis is caused by specific types of bacteria, subsequent studies have focused on finding

out if there is a relationship between changes in the microbiota of the oral cavity and pancreatic cancer.

J.J. Farrell et al. saliva samples were taken from patients with pancreatic cancer, CP, as well as healthy. The results showed significant variability in microflora profiles; in particular, in patients with pancreatic cancer, the number of Neisseria elongata and Streptococcus mitis significantly decreased compared with healthy patients, while the number of Granulicatella adiacens in the group with cancer was increased [35]. These data may be associated with periodontitis. First, since S. Mitis is considered to be a protectant against carcinogenic bacteria, the loss of S. Mitis colonies may be associated with aggressive periodontitis. On the other hand, G. Adiacens, which is a conditionally pathogenic microorganism, may be associated with persistent inflammation, which will ultimately lead to an increased risk of cancer. It is noteworthy that the microbiological profile of saliva samples in patients with pancreatic cancer and CP is different. The main question is whether these changes in the microflora of the oral cavity are involved in carcinogenesis of the pancreas, whether they are secondary to other factors associated with pancreatic cancer, or whether they are a consequence of already developed pancreatic cancer [52].

A large number of studies examine the relationship between Hp infection and pancreatic cancer. Studies and several meta-analyzes have been carried out in which the coefficient of seropositive response to Hp and, in some studies, the presence of Cag A in pancreatic cancer and in the control groups were investigated. Two recent meta-analyzes summarized these studies. In the first meta-analysis, the frequency of a seropositive reaction to HP was higher in patients with pancreatic cancer than in the control groups. However, this ratio only had borderline validity, and it was stronger in studies conducted in Europe and East Asia, and was lower in North America. A positive reaction to Cag A, in contrast, was not associated with a risk of pancreatic cancer [97]. According to the results of the second meta-analysis, which included later studies, but excluding those mentioned in the first meta-analysis, it was concluded that Hp infection and a positive reaction to Cag A are associated with a decrease in the risk of pancreatic cancer in the Asian population, but do not have significant relationships in Western European countries [95]. These conflicting results were most likely obtained due to the heterogeneity of the studies under consideration, the relatively small number of cases included in them, the retrospective nature of most of them, and the possible distortion regarding the relationship between Hp infection and well-established risk factors for pancreatic cancer.

In fact, Hp is associated with lower socioeconomic status, tobacco smoking, alcohol abuse and related diseases such as obesity and diabetes, all of which are risk factors for pancreatic cancer [59], and not all studies have been adjusted according with these variables [52].

An even more recent prospective study examined the relationship between HP and pancreatic cancer. At the starting point of the study, antibodies against Hp and Cag A, as well as pepsinogen I and II in the blood serum were examined in 9506 men and women aged 50-75 years, and their dynamics were monitored for 10 years. During this period, 46 cases of pancreatic cancer were diagnosed, but there was no relationship with Hp (OR=1.32; 95% CI: from 0.73 to 2.39), as well as with a seropositive reaction to Cag A and with changes in levels pepsinogen [28].

In another controlled study, 448 cases of pancreatic cancer were analyzed and after adjusting the most possible distorting factors, it was found that a seropositive reaction to Hp was not associated with pancreatic cancer (OR=0.96; 95% CI: 0.70 to 1.31), as well as was associated with a seropositive reaction to Cag A (OR=1.07; 95% CI: 0.77 to 1.48). A decrease in pepsinogen I, suggesting the presence of atrophic gastritis, with only borderline reliability was associated with an increased risk of pancreatic cancer (OR=1.35; 95% CI: 0.7 to 2.37), and this risk was especially noted among people with seronegative reaction to both Hp and Cag A (OR=5.66; 95% CI: 1.59 to 20.19, P interaction <0.01) [47].

The mechanisms by which the association of Hp with an increased risk of pancreatic cancer can be explained is not clear. H.A. Risch et al. It was suggested that the hypothetical carcinogenic

effect of Hp could be mainly attributed to colonization of the stomach, resulting in increased secretion, increased gastric and duodenal acidity, resulting in increased production of N-nitrosamine or N-nitrosamide, which will act as potential carcinogens on pancreas [76].

According to the 2017 meta-analysis, pancreatic cancer in the intestinal microbiota is characterized by a decrease in the number of Neisseria elongate, Streptococcus mitis and an increase in the number of Porphyromonas gingivalis and Granulicatella adiacens [60]. These data require further explanation and resolution of the issue of their consideration in treatment.

The results of the L.T. study should be taken into account. Geller et al., Who found bacteria in the pancreatic adenocarcinoma tissue (most likely translocation from the intestine), the vital products of which may be the cause of resistance to one of the main chemotherapy drugs, gemcitabine [39].

Recent data indicate a connection between the microbiota of the oral cavity, plaque of the tongue with pancreatic adenocarcinoma. In a case-control population-based study, 361 patients with pancreatic cancer were examined. Oral microbiota was studied by polymerase chain reaction. An increased risk of the disease was found in the presence of Porphyromonas gingivalis in the oral cavity — OR presence/absence of 1.60, 95% CI 1.15–2.22; Aggregatibacter actinomycetemcomitans — OR presence/absence 2.20, 95% CI 1.16–4.18. The authors concluded that oral microbiota may be important in increasing the risk of pancreatic cancer [34].

Another case-control study included 30 patients with pancreatic cancer, 35 with hepatocellular carcinoma, and 25 healthy. The microbiota of the plaque of the tongue was also investigated by the method of polymerase chain reaction. It was found that in pancreatic cancer there is an excess of Leptotrichia, Fusobacterium, Rothia, Actinomyces, Corynebacterium, Atopobium, Peptostreptococcus, Catonella, Oribacterium, Filifactor, Campylobacter, Moraxella and Tannerella compared to healthy ones. Haemophilus, Porphyromonas, Leptotrichia and Fusobacterium — are present in pancreatic cancer, but not in healthy ones. Streptococcus and Absconditabacteria were found in pancreatic cancer, but not in hepatocellular carcinoma. Conclusion: the microbiota of the tongue may be of importance in the early diagnosis of pancreatic cancer and in the differential diagnosis of hepatocellular carcinoma [56].

All the mechanisms discussed above are presented in the final Table 1 and Fig. 3.

Fig. 3. The mechanisms of intestinal microbiota participation in the pathogenesis of major pancreatic diseases (V.S. Akshintala et al., 2019 [13])

We finish the presentation of the role of intestinal microbiota in pancreatic pathology with the words of the Nobel Prize laureate I.M. Mechnikov: "Numerous associations of microbes that inhabit the human intestines largely determine his spiritual and physical health".

Table 1

Possible mechanisms linking the human intestinal microbiome with the pathogenesis and course of pancreatic diseases (C. Loguerici, 2018 [52])

Diseases	Microbiota role	Result
AP	Translocation of symbiotic intestinal bacteria	Pancreatic and systemic infections
AIP	Homology between Helicobacter pylori antigens and harmful proteins	Trigger mechanism for autoimmune response
CP	Excessive growth of small intestinal bacteria	Deterioration of symptoms and nutritional status
Pancreatic cancer	Intestinal dysbiosis associated with chronic inflammation, diabetes and obesity	Factors associated with an increased risk of pancreatic cancer
Pancreatic cancer	Periodontal disease and related changes in the microbiome of the oral cavity	Increased risk of pancreatic cancer
Pancreatic cancer	Helicobacter pylori infection with fundic atrophy and decreased acid secretion or previous gastrectomy	Increased risk of pancreatic cancer due to an increase in the compounds of N-nitroso-(N-nitrosobutylethylamine, N-nitroso-N-ethylvinylamine, N-nitrosodiisopropylamine, N-nitrosodipentylamine) and gastrin

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Intestinal microbiota and pancreatic diseases

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The article presents a detailed literature review on the role of intestinal dysbiosis, including bacterial overgrowth syndrome, as well as increasing intestinal permeability in the pathogenesis of the main pancreatic diseases: acute and chronic pancreatitis (AP and CP), autoimmune pancreatitis, pancreatic cancer.

Thus, according to the results of meta-analysis, populations of *Enterobacteriaceae* and *Enterococcus* were larger in all patients with AP as compared with healthy. There was no difference between the groups with severe and mild AP. Number of *Bifidobacterium* was lower in all patients with AP as compared with healthy. In severe AP, level of endotoxin and cytokines in blood was higher than in mild AP and in healthy.

Participation of *Helicobacter pylori* in pathogenesis of autoimmune pancreatitis via molecular mimicry is assumed. In addition, Helicobacter pylori may have significance in development of pancreatic adenocarcinoma.

In CP, rate of syndrome of bacterial overgrowth has been studied in numerous studies, since dysbiosis halts the effect of enzyme preparations, causes worsening of clinical manifestations. According to the results of meta-analysis, patients with CP are characterized by quantitative and qualitative changes in the composition of intestinal microbiome: decrease of *Bifidobacterium* and *Lactobacillus*, and increase of *Enterobacteriaceae*. The authors also preseented their own data.

Recent data suggest a connection between the oral microbiota, tongue plaque and pancreatic adenocarcinoma. Pancreatic cancer is characterized by decrease of *Neisseria elongate*, *Streptococcus mitis*, and increase of *Porphyromonas gingivalis* and *Granulicatella adiacens*. Recent reports have found that oral microbiota may be important in increasing the risk of pancreatic cancer. The conclusion is drawn on the prospects of studying the intestinal microbiota in pancreatic diseases and the need for its participation in the pathogenesis of this disease.