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Case Report

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Microbiome of the Initial Small Intestine in Patients With Severe Acute Pancreatitis: a Pilot Study

V.V. Kiselev[1] ✉, S.I. Koshechkin[2], A.V. Kurenkov[1], V.E. Odintsova[2], M.S. Zhigalova[1], A.V. Tyakht[3], S.S. Petrikov[1, 4], P.A. Yartsev[1]

Department of Emergency Surgery, Endoscopy and Intensive Care
[1] N.V. Sklifosovsky Research Institute for Emergency Medicine
Bolshaya Sukharevskaya Sq. 3, Moscow, Russian Federation 129090
[2] Nobias Technologies
Berezovaya Alley Str., 14B, bldg. 2, pom. 2/4, Moscow, Russian Federation 127273
[3] Institute of Gene Biology Russian Academy of Sciences
Vavilova Str., 34/5, Moscow, Russian Federation 119334
[4] Russian University of Medicine, N.D. Yushchuk Scientific and Educational Institute of Continuous Professional Education
Dolgorukovskaya, St. 4, Moscow, Russian Federation 127006

✉ **Contacts:** Vladimir V. Kiselev, Candidate of Medical Sciences, Leading Researcher at the Department of Emergency Surgery, Endoscopy and Intensive Care of the N.V. Sklifosovsky Research Institute for Emergency Medicine. Email: kiselevvv@sklif.mos.ru

ABSTRACT Disruption of intestinal homeostasis is a leading factor in the pathogenesis and progression of systemic inflammation in patients with acute severe pancreatitis. The development of systemic complications occurs due to both mesenteric hypoperfusion and dysregulation of intestinal motility, as well as destruction of the intestinal barrier, with translocation of bacterial bodies and their substrates. This increases the risk of developing multiple organ failure and increased mortality. With the advent of high-throughput sequencing methods for microbiome samples, for example, in the 16S rRNA format, the possibilities for studying the structure of microbial communities have expanded significantly. In this regard, there is increasing evidence of the relationship between human health and the microflora inhabiting various parts of the body.

AIM OF THE STUDY Description of the microbiota composition of the initial sections of the small intestine in patients with severe acute pancreatitis.

MATERIAL AND METHODS The study included 7 patients with a diagnosis of severe acute pancreatitis (6 men, 1 woman), the average age was 54.1±14.4 years. Patients were divided into two groups. Group 1 (n=4) included patients admitted on the 2nd–4th day from the onset of a pain attack. Group 2 (n=3) included patients admitted no later than 24 hours from the onset of the disease. The bacterial composition of jejunal swab samples was studied using 16S RNA sequencing. The severity of the condition was assessed using the integral APACHE II, SOFA, SAPS II scales. In patients of the main group, APACHE II was score 22±2.83, SOFA was score 6.8±0.5, SAPS II was score 32.9±6.4, in patients of the comparison group, APACHE II was score 18.0±3.7, SOFA was score 4.0±2.6, SAPS II was score 24.4±5.0.

The material was collected at the time of insertion of a sterile multifunctional intestinal catheter behind the Treitz ligament, no later than 6 hours after admission to the intensive care unit. At the time of material collection, the patients did not receive antibacterial therapy or enteral nutrition.

RESULTS More severe disease was associated with reduced representation of Nesseria species in the microbiome mucosa and parvimonas micra, inhabiting the mucosal layer, as well as Megasphaera micronuciformis. The proportion of the genera Streptococcus (species S. rubneri / parasanguinis / australis) and Actinomyces and a number of genera from the Enterobacteriaceae family in such patients was, on the contrary, higher.

Keywords: intestinal lavage, microbiome, severe acute pancreatitis, saline enteral solution, intestinal barrier

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Affiliations

Vladimir V. Kiselev	Candidate of Medical Sciences, Leading Researcher, Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-0170-7775, kiselevvv@sklif.mos.ru; 25%, project management, development of the concept, design and methodology of the research, conducting the research and analyzing the obtained data, preparing and editing the text of the article
Stanislav I. Koshechkin	Candidate of Biological Sciences, Director for Science, Nobias Technologies; https://orcid.org/0000-0002-7389-0476, st.koshechkin@gmail.com; 15%, management, coordination, planning and implementation of the laboratory part of the study

Alexey V. Kurenkov	Physician and Endoscopist, Endoscopy and Intraluminal Surgery Department, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-6617-1967, oky-doker@yandex.ru; 15%, development of methodology and implementation of research
Vera E. Odintsova	Head of Analysis Department, Nobias Technologies; https://orcid.org/0000-0003-1897-4033, vera.odints@gmail.com; 15%, participation in statistical data processing and writing the text of the article
Maria S. Zhigalova	Candidate of Medical Sciences, Senior Researcher, Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-4520-1124, zhigalovams@sklif.mos.ru; 10%, development of the concept and design of the study, analysis of the obtained data, preparation and editing of the text of the article
Aleksandr V. Tyakht	Candidate of Biological Sciences, Research Fellow, Institute of Gene Biology Russian Academy of Sciences; https://orcid.org/0000-0002-7358-2537, a.tyakht@gmail.com; 10%, participation in the design of the study, interpretation of the results of statistical data processing and writing the text of the article
Sergey S. Petrikov	Corresponding Member of the RAS, Professor, Doctor of Medical Sciences, Director of N.V. Sklifosovsky Research Institute for Emergency Medicine, Head of the N.D. Yushchuk Department of Anesthesiology, Resuscitation and Emergency Medicine of the Scientific and Educational Institute of Continuous Professional Education, Russian University of Medicine; https://orcid.org/0000-0003-3292-8789, petrikovss@sklif.mos.ru; 5%, consulting and editing the text of the article
Pyotr A. Yartsev	Professor, Doctor of Medical Sciences, Head of the Scientific Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency; https://orcid.org/0000-0003-1270-5414, yartsevpa@sklif.mos.ru; 5%, consulting and editing the text of the article

GIT — gastrointestinal tract
IAP — intra-abdominal pressure
ICU — intensive care unit

INTRODUCTION

Impaired intestinal homeostasis is a leading factor in the pathogenesis and progression of the systemic inflammatory response in patients with acute severe pancreatitis. In turn, systemic complications develop as a result of mesenteric hypoperfusion and dysregulation of intestinal motility, as well as destruction of the intestinal barrier with translocation of bacterial bodies and their substrates. It is worth noting that all of the above processes increase the risk of multiple organ failure, leading to an increase in fatal outcomes [1]. With the advent of high-throughput sequencing methods for microbiome samples, such as 16S rRNA, the possibilities for studying the structure of microbial communities have expanded significantly. In this regard, there is increasing evidence of the relationship between human health and the microflora inhabiting various parts of the body.

IFS — intestinal failure syndrome
SES — saline enteral solution

The commensal microflora in the small intestine of a healthy person consists of approximately 10^3 – 10^4 different species of bacteria. They are essential for the digestion of food substrates, participate in the generation of secondary bile acIFS, which promote - the absorption of dietary lipIFS and fat-soluble vitamins [2], have a proliferative effect on intestinal epithelial cells, promote the differentiation of enterocytes, prevent colonization by pathogenic microorganisms and form a local and systemic immune response [3]. Fermentation of complex carbohydrates results in the formation of short-chain fatty acIFS, which serve as a source of energy for the macroorganism and have a beneficial effect on immune cells [4], proliferation, differentiation and function of intestinal epithelial cells [5], and participate in the regulation of metabolism [6]. Thus, intestinal microbiota and its metabolic products are vital for intestinal homeostasis.

Numerous clinical and experimental studies demonstrate that pancreatic ischemia plays an important role in the development of acute pancreatitis and disease progression with further development of pancreatic necrosis [7–9]. Microcirculation disorders are caused by decreased capillary blood flow in the pancreatic tissues against the background of inflammation. Hypotension associated with systemic inflammatory response syndrome usually leads to centralization of blood circulation due to shunting of blood from peripheral vessels to the main bloodstream. The small intestine is involved in microcirculatory disorders, resulting in neuroendocrine dysregulation and epithelial dysfunction of enterocytes, which are an important source of proinflammatory mediators such as interleukin-17, lipid mediators produced by phospholipase A2 and antimicrobial peptides [10, 11]. At the same time, an increase in the proportion of pathogenic microorganisms in the small intestinal microbiota leads to bacterial overgrowth syndrome and translocation of microbial substrates. Bacterial translocation and bacteremia lead to further escalation of systemic inflammation, and in some cases to the development of sepsis, septic shock and circulatory failure with multiple organ dysfunction syndrome [10].

Diagnosis and treatment of intestinal failure syndrome (IFS) is a complex task, since intestinal dysfunction and gastrointestinal (GI) failure develop in the most severe patients with a long stay in the intensive care unit (ICU) [12]. Instrumental methods for detecting IFS manifestations remain complex, and laboratory markers do not always reflect the real picture of critical events in the small intestine [1, 13–16]. With the advent of high-throughput sequencing methods for microbiome samples, such as 16S rRNA, the possibilities for studying the structure of microbial communities have expanded significantly. In this regard, there is increasing evidence of the relationship between human health and the microflora inhabiting various parts of the body. DNA analysis of the microbiome provides new opportunities for early correction of intestinal microbiota disorders and prevention of IFS development, including in critically ill individuals.

Currently, there are data on the colon microbiome in patients with varying degrees of pancreatitis severity [16]. However, a more accurate picture of changes should be expected in the small intestine microbiota. In this work, the microbial composition of the jejunum is studied. Samples were obtained from 7 patients with acute pancreatitis of varying severity. In particular, a comparison was made of two samples taken from one patient with a difference of 24 hours against the background of enteral infusion of saline enteral solution (SES).

MATERIAL AND METHODS

Patient recruitment and swab sample collection

The study included 7 patients (6 men, 1 woman, age 54.1±14.4 years) with severe acute pancreatitis confirmed by computed tomography and ultrasound studies. The etiological cause of the development of this disease was the alcohol factor. All patients had abdominal pain, nausea, vomiting, increased levels of pancreatic enzymes in the blood serum.

The patients were divided into two groups: the first group ($n = 4$, main group) included patients who were admitted on the 2nd–4th day from the onset of the disease (from the onset of the pain attack). The second group ($n = 3$, comparison group) included patients who were admitted no later than 24 hours from the onset of the disease.

The severity of the condition was assessed using *APACHE* II, *SOFA* , *SAPS* II. Patients in the main group admitted on days 2-4 from the onset of the disease had higher scores on the integral severity scales: *APACHE* II — 22±2.83 points, *SOFA* — 6.8±0.5 points, *SAPS* II — 32.9±6.4 points compared to patients in the comparison group *APACHE* II 18.0±3.7 points, *SOFA* — 4.0±2.6 points, *SAPS* II — 24.4±5.0 points.

All patients examined underwent intestinal microbiota analysis using jejunal swab samples. The material for the study was collected at the time of insertion of a sterile multifunctional intestinal catheter (patent for utility model "Multifunctional intestinal catheter", RU 199398 U1, 08/31/2020) through the Treitz ligament, no later than 6 hours after admission to the intensive care unit. At the time of material collection, the patients did not receive

antibacterial therapy and enteral nutrition. The installation of the probe with location control and collection of material were performed using the *EXERA* II *SIF-Q* 180 video endoscopic system (*Olympus*) using an original technique that excludes contamination of the test material with microorganisms from other biological environments (patent for utility model "Method for collecting biological fluid from the small intestine through an endoscopic channel", RU 2738007 C1, 04/29/2020). All patients in the study groups were given SES for enteral infusions (Patent RU 2 699 22 C1 dated 09/04/2019) into the intestinal tube to stimulate intestinal motility and enteral correction of microbiota. The SES contains pectin, inulin and glutamine. In the main group, the introduction of SE was carried out at a rate of 6-10 ml per minute, in a volume of 1500 (±412.3) ml, provided that the intra-abdominal pressure (IAP) did not exceed 16-20 mm Hg. IAP was measured using the method recommended by the World Society for the Study of Intra-Abdominal Hypertension (*WSACS*).

Microbiome Analysis

DNA extraction was performed using the *DNeasy PowerLyzer Microbial kit* (*Qiagen*). Sequencing libraries were prepared for the V4 hypervariable region of the 16S rRNA gene as described in medical journals [17]. Sequencing was performed on the *Illumina MiSeq platform*. Sequencing data (reads) were processed in the Knomics-Biota online system [18]. The complete taxonomic composition of the microbiome of each sample was obtained using the *DADA* 2 algorithm [19]. Refinement of the taxonomic classification for the most represented DNA sequences was performed using the *BLAST algorithm* on *the NCBI database. nr* (*https://blast.ncbi.nlm.nih.gov/Blast.cgi*). In case a sequence with complete identity mapped to several taxa, all of them were indicated in the name (e.g. *Streptococcus rubneri/parasanguinis/australis*). Taxonomic composition was estimated from unthinned data. Microbiota alpha diversity was obtained after 5-fold random thinning to 3000 reads and averaging the results. The distance between samples was estimated using the Aitchison distance on unthinned data.

To determine the degree of contamination of the samples during sequencing, the taxonomic composition of the samples was compared with three negative control samples. Overall, contamination was insignificant. Taxa that were well represented in the negative control but poorly represented in the studied samples were excluded from the sample composition. Some of the taxa present in the negative control were retained in further analysis, since their possible presence in the intestinal microbiota has been described in the literature. Their presence in the microbiota of patients with acute pancreatitis will be tested in subsequent studies with a larger sample.

In order to describe the differences between the groups, an additional analysis was performed in the *R development environment* [20]. *The clr* transformation was applied to the taxa representations [21]. This approach considers not the proportions of each bacterium in the microbial community, but their ratios to a certain average proportion of microbes in the sample on a logarithmic scale. This approach allows for a more correct assessment of the differences between the samples [22]. Only those bacteria that were present in all samples of at least one of the groups were taken into account. Replacement of zero values of representation was performed using the *cmultRepl function of the zCompositions* library [23]. In order to assess which taxa differed most between the groups, bacteria were selected whose representation in all samples of one group was higher than their representation in samples of the other group. Fisher's test with Benjamini–Hochberg multiple comparison correction was used to compare the representation of taxa in two samples of the same patient. The analysis was performed at the genus and unique read levels. The taxonomy of the reads was then refined to species using the *BLAST algorithm* against *the NCBI nr database*.

RESULTS

Description of the microbial composition of jejunal swabs

The taxonomic composition of the samples is shown in Fig. 1, *S* 1. Streptococci were the most numerous in the microbiota. They are represented by a wide range of species, including *Streptococcus oralis/cristatus/mitis/infantis/gordonii*, *rubneri/parasanguinis/australis*, *anginosus*, *mutans*, *thermophilus/salivarius/vestibularis* and closely related unclassified species. They belong to the normal flora of the upper gastrointestinal tract of humans, including the small intestine [24]. Most of them belong to the *S. mitis group*. In some studies, a decrease in antibodies to *S. mitis* in blood plasma, as well as a reduced representation of the bacterium itself in saliva, was associated with pancreatic cancer [25].

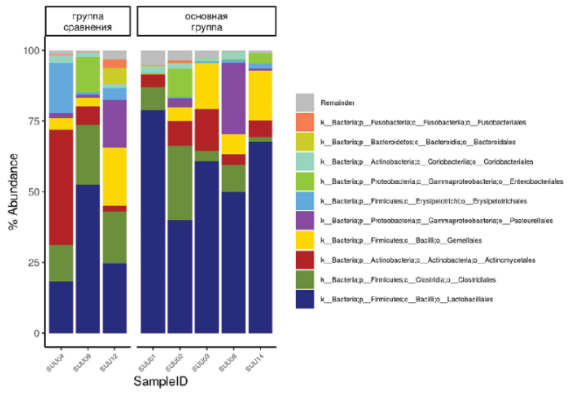

Fig. 1. Taxonomic composition of samples at the order level. Sample SUU 02 is the second sample of one of the patients of the main group. The first sample of this patient is SUU 01

Fig. S1. Heat map of taxa abundance (before manual removal of negative control reads)

Unclassified representatives of the *Gemellaceae family were present in all samples*. Their taxonomic affiliation was clarified as the species *Gemella taiwanensis/parahaemolysans/sanguinis/morbillorum/haemolysans*. These species belong to the normal flora of the small intestine [24].

Peptostreptococcus and *Solobacterium* were observed in all samples. According to the *NCBI database*, they are represented by the species *P. stomatis* and *Solobacterium moorei*. Their increased representation in stool is associated with colorectal cancer [26].

The genus *Haemophilus* was represented by the species *H. hae molyticus* and *parainfluenzae*. *Haemophilus haemolyticus* is an upper respiratory tract infection pathogen associated with chronic obstructive pulmonary disease [27], but in some cases it was isolated from the blood of patients with bacteremia [28]. *H. parainfluenzae* is mainly a pulmonary and upper respiratory tract infection pathogen, capable of causing bacteremia and infective endocarditis. It was also detected during a study of the intestinal microbiota of patients with various diseases, including irritable bowel syndrome [29] and gastric cancer [30]. The genus *Haemophilus* was present in small quantities in the negative control.

Among the taxa with high representation was the genus *Corynebacterium* - in one of the samples of the comparison group its share was 36.9%. The detection was specified as *C. argentoratense* or a closely related bacterium. This is a microbe found initially in the upper respiratory tract [31], and then in other parts of the body, including in infections [32].

Unclassified members of the *Enterobacteriaceae family were also observed in several patients*; although the gene region corresponding to them did not allow for unambiguous identification of the taxon to the genus level, this family is known to include, among others, such opportunistic pathogens as *Escherichia/Shigella* and *Klebsiella* .

The patients also had such representatives of normal flora as *Rothia* (including *mucilaginosa* and *dentocariosa*), *Granulicatella*, *Parvimonas*, *Veilonella* and *Actinomyces* (specified as *A. odontolyticus*).

The Shannon index varied from 2.73 to 4.4 (Fig. 2). It characterizes the uniformity of representation of different taxa in the microbiota. The *Chao* 1 index, which characterizes the diversity of the microbiota and the representation of rare species in it, varied from 72.32 to 132.01. The Aitchison distance between samples varied from 5.46 to 21.56.

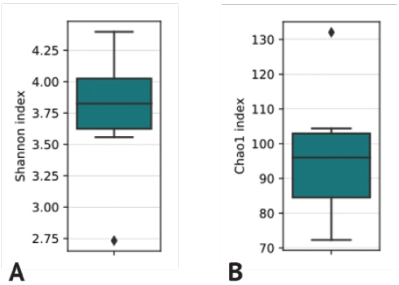

Fig. 2. Alpha diversity in patients with acute pancreatitis: A — Shannon index; B — Chao1 index

Gut swab microbiota is associated with clinical status

The microbial composition of the swabs also differed between the study group and the comparison group. Among the most common microbes, the greatest differences in representation between the study and comparison groups were observed for *Streptococcus rubneri/parasanguinis/australis*: its proportion was higher in patients of the study group (Fig. 3). These species belong to the *S. mitis group* and are part of the normal flora of the intestine and oral cavity. However, streptococci of this group, entering the bloodstream, can cause bacteremia, endocarditis and other diseases [33]. In the study group, opportunistic taxa *Actinomyces* [34] and *Escherichia/Shigella* (or closely related *Brenneria/Pseudescherichia*) were also more represented. Among the bacteria, the proportion of which was reduced in the samples of the study group were *Neisseria mucosa*, which lives in the intestinal mucosa [35], and *Parvimonas micra*, which degrades mucin [36, 37]. The representation of *Megasphaera micronuciformis* was also reduced (Fig. 3) [38, 39].

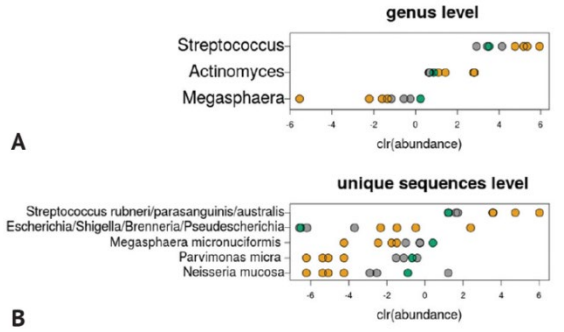

Fig. 3. Clr-transformed abundance of individual (A) genera, (B) unique sequences. Samples from participants in the main group are shown in yellow, samples from the comparison group are shown in gray. Sample SUU 02, taken again from a patient from the main group, is shown in green

Comparison of two samples in a patient of the main group before and after the introduction of enteral saline solution

Two samples were taken from one patient in the main group. The first was obtained during endoscopic placement of a multifunctional intestinal catheter. A second sample was taken 24 hours later during re-insertion due to dislocation of the initially placed catheter.

In this sample, the abundance of the taxa listed in the previous section was closer to the abundance in the comparison group samples than to the values for the main group samples (Fig. 3). *Parvimonas micra*, *Neisseria mucosa*, and *Megasphaera micronuciformis* were not detected in the first patient's sample and were found in significant quantities in the second (*N. mucosa* - 0.34%, *P. micra* - 0.43%, *M. micronuciformis* - *1.3%). The relative abundance of Streptococcus Rubneri/parasanguinis/australis* decreased (from 24.58 to 2.93%), as well as the proportion of the entire genus *Streptococcus* (from 46.09 to 34.73%), the genus *Actinomyces* (from 3.69 to 2.45%), and *Escherichia/Shigella/Brenneria/Pseudescherichia* (from 0.36 to 0%). To exclude the possibility that the observed difference was due to variability in the sequencing depth of the samples, Fisher's exact test was performed for each of the bacteria. The results of the test confirm that the differences between the two samples are not random ($p < 0.05$).

In terms of beta diversity (Aitchison distance), the data from the second sample also turned out to be closer to the comparison group than to the main one (Fig. 4) and were more similar to the samples of patients with a lower severity level than to the first sample of the subject.

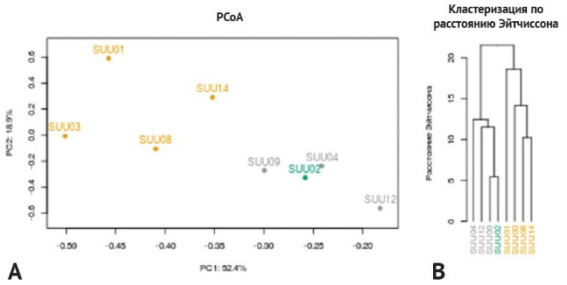

Fig. 4. Visualization of beta diversity analysis (Aitchison distance between samples): A — using principal component analysis in clr-coordinates, B — using clustering of samples by the distance between them. Samples from participants in the main group are shown in yellow, samples from the comparison group are shown in gray. Sample SUU 02, taken again from a patient from the main group, is shown in green

CONCLUSION

In the course of the study, microbes found in the swab samples were mainly those identified in other studies of the microbiota of different parts of the small intestine. Many of these microbes are also determined in the oral cavity and colon. Although these bacteria are commensal, when they enter the bloodstream, they can cause bacteremia and infectious-bacterial complications of target organs. Several bacteria were detected in both swab and negative control samples. Their presence in the microbiota of patients with severe acute pancreatitis should be verified in further studies with a larger sample size.

Comparison of patients with different severity of the disease indicates a decrease in the proportion of bacteria living in the mucosa in patients with higher scores according to the integral severity scales. This may be evidence of a connection between complications of acute pancreatitis and a decrease in the mucosal layer. Such a decrease can potentially lead to a decrease in the protective functions of the intestine, and in the case of reperfusion, to bacterial translocation through damaged structures of the intestinal wall and the development of systemic complications.

This is a pilot study. A larger sample is planned to verify its results. It is also necessary to study the jejunal microbiota of healthy people in order to be able to assess the changes caused by acute pancreatitis. However, the results of the pilot study show that the methodology is generally valid.

FINDINGS

1. The obtained results indicate that the study of the small intestinal microbiome in patients with severe acute pancreatitis may be of critical importance for an expanded understanding of both normal and pathological processes of the upper - gastrointestinal tract, which are fundamental in the development of organ dysfunction.

2. A more severe course of severe acute pancreatitis is associated with a reduced representation in the microbiome of *Nesseria mucosa* and *Parvimonas micra species* inhabiting the mucosal layer, as well as *Megasphaera micronuciformis*, which may indicate dysfunction of intestinal epithelial cells in the early stages of severe acute pancreatitis.

3. A decrease in the proportion of bacteria living in the mucous membrane in patients with a more severe course of the disease is of scientific and practical interest and requires further study in an expanded cohort of patients with severe acute pancreatitis.

4. Conducting specific enteral therapy can probably have a protective effect on intestinal epithelial cells and prevent further progression of bacterial overgrowth syndrome and intestinal failure.

REFERENCES

1. Dibirov MD, Isaev AI, Djadjiev AB, Ashimova AI, Ataev T. Role of correction of the syndrome of intestinal failure and abdominal hypertension in the prevention of infection of pancreatic necrosis. *Pirogov Russian Journal of Surgery*. 2016;(8):67 72. (In Russ.) https://doi.org/10.17116/hirurgia2016867-72
2. Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, et al. Gut microbiota functions: metabolism of nutrients and other food components. *Eur J Nutr*. 2018;57(1):1–24. PMID: 28393285 https://doi.org/10.1007/s00394-017-1445-8
3. Yu L.C. Microbiota dysbiosis and barrier dysfunction in inflammatory bowel disease and colorectal cancers: exploring a common ground hypothesis. *J Biomed Sci* . 2018;25(1):79. PMID: 30413188 https://doi.org/10.1186/s12929-018-0483-8
4. Yu LC, Wang JT, Wei SC, Ni YH. Host-microbial interactions and regulation of intestinal epithelial barrier function: From physiology to pathology. *World J Gastrointest Pathophysiol.* 2012;3(1):27–43. PMID: 22368784 https://doi.org/10.4291/wjgp.v3.i1.27
5. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol*. 2016;16(6):341–352. PMID: 27231050 https://doi.org/10.1038/nri.2016.42
6. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty AcIFS as Key Bacterial Metabolites. *Cell* . 2016;165(6):1332–1345. PMID: 27259147 https://doi.org/10.1016/j.cell.2016.05.041.
7. Grootjans J, Lenaerts K, Buurman WA, Dejong CH, Derikx JP. Life and death at the mucosal-luminal interface: New perspectives on human intestinal ischemia-reperfusion. *World J Gastroenterol*. 2016;22(9):2760–2770. PMID: 26973414 https://doi.org/10.3748/wjg.v22.i9.2760
8. Ji Y, Luo X, Yang Y, Dai Z, Wu G, Wu Z. Endoplasmic reticulum stress-induced apoptosis in intestinal epithelial cells: a feed-back regulation by mechanistic target of rapamycin complex 1 (mTORC1). *J Anim Sci Biotechnol* . 2018;9:38. PMID: 29744053 https://doi.org/10.1186/s40104-018-0253-1
9. Schellekens DH, Hundscheid IH, Leenarts CA, Grootjans J, Lenaerts K, Buurman WA, et al. Human small intestine is capable of restoring barrier function after short ischemic periods. *World J Gastroenterol*. 2017;23(48):8452–8464. PMID: 29358855 https://doi.org/10.3748/wjg.v23.i48.8452
10. Manohar M, Verma AK, Venkateshaiah SU, Sanders NL, Mishra A. Pathogenic mechanisms of pancreatitis. *World J Gastrointest Pharmacol Ther*. 2017;8(1):10–25. PMID: 28217371 https://doi.org/10.4292/wjgpt.v8.i1.10
11. Lin R, Chen F, Wen S, Teng T, Pan Y, Huang H. Interleukin-10 attenuates impairment of the blood-brain barrier in a severe acute pancreatitis rat model. *J Inflamm (Lond)* . 2018;15:4. PMID: 29497350 https://doi.org/10.1186/s12950-018-0180-0
12. Sertaridou E, Papaioannou V, Kolios G, Pneumatikos I. Gut failure in critical care: old school versus new school. *Ann Gastroenterol*. 2015;28(3):309–322. PMID: 26130136
13. Reintam Blaser A, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. *Intensive Care Med* . 2012;38(3):384–394. PMID: 22310869 https://doi.org/10.1007/s00134-011-2459-y
14. Schmidt PN, Roug S, Hansen EF, Knudsen JD, Novovic S. Spectrum of microorganisms in infected walled-off pancreatic necrosis – impact on organ failure and mortality. *Pancreatology* . 2014;14(6):444–449. PMID: 25266641 https://doi.org/10.1016/j.pan.2014.09.001
15. Xiao H, Huang JH, Zhang XW, Ahmed R, Xie QL, Li B, et al. Identification of potential diagnostic biomarkers of acute pancreatitis by serum metabolomic profiles. *Pancreatology* . 2017;17(4):543–549. PMID: 28487129 https://doi.org/10.1016/j.pan.2017.04.015.
16. Yu S, Xiong Y, Fu Y, Chen G, Zhu H, Mo X, et al. Shotgun metagenomics reveals significant gut microbiome features in different grades of acute pancreatitis. *Microb Pathog* . 2021;154:104849. PMID: 33781869 https://doi.org/10.1016/j.micpath.2021.104849.
17. Andrianova NV, Popkov VA, Klimenko NS, Tyakht AV, Baydakova GV, Frolova OY, et al. Microbiome-Metabolome Signature of Acute Kidney Injury. *Metabolites*. 2020;10(4):142. PMID: 32260384 https://doi.org/10.3390/metabo10040142
18. Efimova D, Tyakht A, Popenko A, Vasilyev A, Altukhov I, Dovidchenko N, et al. Knomics-Biota – a system for exploratory analysis of human gut microbiota data. *BioData Min* . 2018;11:25. PMID: 30450127 https://doi.org/10.1186/s13040-018-0187-3
19. Callahan BJ, McMurdie PJ, Rosen MJ, Han AW, Johnson AJ, Holmes SP. DADA2: High-resolution sample inference from Illumina amplicon data. *Nat Methods*. 2016;13(7):581–583. PMID: 27214047 https://doi.org/10.1038/nmeth.3869
20. Horton NJ, Kleinman K. *Using R and RStudio for Data Management, Statistical Analysis, and Graphics*. New York: ImprintChapman and Hall/CRC; 2015. https://doi.org/10.1201/b18151
21. Aitchison J. *The Statistical Analysis of Compositional Data.* London: Chapman and Hall; 1986. https://doi.org/10.1007/978-94-009-4109-0
22. Gloor GB, Macklaim JM, Pawlowsky-Glahn V, Egozcue JJ. Microbiome Datasets are Compositional: and This is Not Optional. *Front Microbiol.* 2017;8:2224. PMID: 29187837 https://doi.org/10.3389/fmicb.2017.02224
23. Palarea-Albaladejo J, Martín-Fernández JA. ZCompositions — R package for multivariate imputation of left-censored data under a compositional approach. *Chemometrics and Intelligent Laboratory Systems*. 2015;143:85–96. https://doi.org/10.1016/j.chemolab.2015.02.019.
24. Villmones HC, Haug ES, Ulvestad E, Grude N, Stenstad T, Halland A, et al. Species Level Description of the Human Ileal Bacterial Microbiota. *Sci Rep* . 2018;8(1):4736. PMID: 29549283 https://doi.org/10.1038/s41598-018-23198-5
25. Akshintala VS, Talukdar R, Singh VK, Goggins M. The Gut Microbiome in Pancreatic Disease. *Clin Gastroenterol Hepatol*. 2019;17(2):290–295. PMID: 30144522 https://doi.org/10.1016/j.cgh.2018.08.045
26. Yu J, Feng Q, Wong SH, Zhang D, Liang QY, Qin Y, et al. Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. *Gut*. 2017;66(1):70–78. PMID: 26408641 https://doi.org/10.1136/gutjnl-2015-309800.
27. Osman KL, Jefferies JMC, Woelk CH, Devos N, Pascal TG, Mortier MC, et al. Patients with Chronic Obstructive Pulmonary Disease harbor a variation of Haemophilus species. *Sci Rep*. 2018;8(1):14734. PMID: 30282975 https://doi.org/10.1038/s41598-018-32973-3
28. Morton DJ, Hempel RJ, Whitby PW, Seale TW, Stull TL. An invasive Haemophilus haemolyticus isolate. *J Clin Microbiol*. 2012;50(4):1502–1503. PMID: 22301029 https://doi.org/10.1128/JCM.06688-11

29. Saulnier DM, Riehle K, Mistretta TA, Diaz MA, Mandal D, Raza S, et al. Gastrointestinal microbiome signatures of pediatric patients with irritable bowel syndrome. *Gastroenterology*. 2011;141(5):1782–1791. PMID: 21741921 https://doi.org/10.1053/j.gastro.2011.06.072
30. Dong Z, Chen B, Pan H, Wang D, Liu M, Yang Y, et al. Detection of Microbial 16S rRNA Gene in the Serum of Patients With Gastric Cancer. *Front Oncol* . 2019;9:608. PMID: 31338330 https://doi.org/10.3389/fonc.2019.00608
31. Riegel P, Ruimy R, De Briel D, Prevost G, Jehl F, Bimet F, et al. Corynebacterium argentoratense sp. nov., from the human throat. *Int J Syst Bacteriol* . 1995;45(3):533–537. PMID: 8590681 https://doi.org/10.1099/00207713-45-3-533.
32. Fernández-Natal I, Sáez-Nieto JA, Rodríguez-Lázaro D, Valdezate-Ramos S, Parras-Padilla T, Medina MJ, et al. Phenotypic, molecular characterization, antimicrobial susceptibility and draft genome sequence of Corynebacterium argentoratense strains isolated from clinical samples. *New Microbes New Infect* . 2016;10:116–121. PMID: 26933505 https://doi.org/10.1016/j.nmni.2016.01.007
33. Chhatwal GS, Graham R. Streptococcal Diseases. In: Quah SR (ed.). *International Encyclopedia of Public Health*. 2nd ed. Academic Press, 2017. pp. 87–97. https://doi.org/10.1016/B978-0-12-803678-5.00434-3.
34. Fonkou MDM, Bilen M, Cadoret F, Fournier PE, Dubourg G, Raoult D. Enterococcus timonensis sp. nov., Actinomyces marseillensis sp. nov., Leptotrichia massiliensis sp. nov., Actinomyces pacaensis sp. nov., Actinomyces oralis sp. nov., Actinomyces culturomici sp. nov. and Gemella massiliensis sp. nov., new bacterial species isolated from the human respiratory microbiome. *New Microbes New Infect* . 2017;22:37–43. PMID: 29556407 https://doi.org/10.1016/j.nmni.2017.12.005.
35. Tønjum T. Neisseriales ord. nov. In: *Bergey's Manual of Systematics of Archaea and Bacteria*. John Wiley & Sons, Inc.; Bergey's Manual Trust, 2015. pp. 1–3. https://doi.org/10.1002/9781118960608.obm00079
36. Dai D, Nanthkumar NN, Newburg DS, Walker WA. Role of oligosaccharides and glycoconjugates in intestinal host defense. *J Pediatr Gastroenterol Nutr.* 2000;30 Suppl 2:S23–33. PMID: 10749398.
37. Carlstedt-Duke B, Midtvedt T, Nord CE, Gustafsson BE. Isolation and characterization of a mucin-degrading strain of Peptostreptococcus from rat intestinal tract. *Acta Pathol Microbiol Immunol Scand B*. 1986;94(5):293–300. PMID: 3788570 https://doi.org/10.1111/j.1699-0463.1986.tb03056.x.
38. Shetty SA, Marathe NP, Lanjekar V, Ranade D, Shouche YS. Comparative genome analysis of Megasphaera sp. reveals niche specialization and its potential role in the human gut. *PLoS One* . 2013;8(11):e79353. PMID: 24260205 https://doi.org/10.1371/journal.pone.0079353
39. Marchandin H, Jumas-Bilak E, Gay B, Teyssier C, Jean-Pierre H, Siméon de Buochberg M, et al. Phylogenetic analysis of some Sporomusa sub-branch members isolated from human clinical specimens: description of Megasphaera micronuciformis sp. nov. *Int J Syst Evol Microbiol*. 2003;53(Pt 2):547–553. PMID: 12710625 https://doi.org/10.1099/ijs.0.02378-0 .

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