Provisional chapter

Microbiota-Oriented Diagnostics and Therapy in Sepsis: Utopia or Necessity?

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Additional information is available at the end of the chapter

Abstract

When diagnosing sepsis, it is common to look for pathogens, microbe's DNA, lipopolysaccharide (LPS), or host biomarkers while missing out on microbiota. The next-generation sequencing of 16S rRNA gene allowed characterizing the gut microbiota taxonomy and clarifying the gut microbial population being more complex than was previously thought. We suppose that significant disruption of the microbiota is an indicator of the major role it plays in sepsis. Serious metabolic disorders of the gut microbiota may contribute to an unfavorable outcome in septic patients. With the changes not only in the composition but also in the metabolic activity of the gut microbiota taken into account, the characteristics of the mechanisms of interactions in the "septic" microbiome will allow the advances in the optimization of the diagnostics and therapy of sepsis to be made.

Keywords: sepsis, gut microbiome, critical states, aromatic microbial metabolites, metabolome, organ dysfunction

1. Introduction

In recent years, the microbiome has been considered as an important player in the pathophysiology of various types of diseases, including trauma and sepsis [1, 2]. Over 70% of species of microorganisms are nonculturable and cannot be isolated as a pure culture for identification. Omics technologies (genomics, transcriptomics, metagenomic sequencing, proteomics, and metabolomics) have fully changed our concepts about the composition and function of the "invisible organ" [3]. Widespread distribution of microbiomic studies became possible about 10 years ago with the emergence of high-performance new-generation sequencing (NGS), allowing transcribing in mass the collective genome of microbiomes—metagenome. The 16S

rRNA gene encodes highly specific RNA of bacterial ribosomes and is present in genomes of all known microorganisms. Its structure is quite conservative, but variable-specific regions allow identifying microorganisms of different species and strains. The study pattern is quite simple but rather laborious: at the first stage, DNA is isolated from a sample, and then a so-called genome library containing copies of gene 16S rRNA belonging to different bacteria is obtained. The library is "read" using high-performance sequenators providing reception of several thousand nucleotide sequences of gene 16S rRNA for each sample. The next stage deals with analysis of a huge body of received data using bioinformatic techniques. Results are represented in a way most suitable in each particular case. The introduction of latest technologies, for example, nanopore sequencing, allows fast identification of bacteria in samples and finding markers of resistance to antimicrobial drugs within 5–10 minutes with the portable real-time device for DNA and RNA sequencing "MinION" that weighs less than 100 grams. This method is currently undergoing clinical testing [4]. However, in a typical microbiome experiment, several aspects of microbial communities still remain inaccessible. These include low-abundance but potentially crucial taxa whose genetic material is not sampled by sequencing techniques due to being present below the level of detection [5]. The real value of all this novel knowledge to understand the pathogenesis of sepsis has yet to be established. In this chapter, we are discussing the important role of bacterial metabolites in comparison with taxonomic structure of the septic gut microbiota.

2. The gap between healthy and septic gut microbiomes

Sepsis is a multifaceted host response to an infecting pathogen that may be significantly amplified by endogenous factors [6]. The broader perspective also emphasizes the significant biological and clinical heterogeneity in affected individuals such as their age, underlying comorbidities, concurrent injuries (including surgery) and medications, and source of infection adding to further complexity [7]. The success of antibiotic treatment depends on rapid and accurate identification of relevant pathogens and is complicated by the increasing rate of antimicrobial resistance conditioned by the dynamic changes in the bacterial population in which aerobic and facultative anaerobic bacteria predominant at the onset of sepsis are replaced by anaerobic species as the oxygen levels deplete. Broad-spectrum therapy is administered in the absence of bacterial identification, but this may not accurately reflect causative pathogens [8].

For a better understanding of how to treat, we probably should change the paradigm from "anthropocentrism" to "microbiocentrism," as we think.

The presence of over hundreds of species in the gut of a healthy adult host is a way to survive in an ever-changing world and the ability to receive energy from different sources of food. In critical condition, the advantage is obtained by those species that are capable of surviving in more extreme conditions with less oxygen and a lack of nutrients and trace elements. For example, *Enterococcus* is one of the few microorganisms capable of surviving and thriving in the presence of bile acids, an increased concentration (6.5%) of NaCl, hydrogen peroxide, and changes in the pH level [9]. The most frequent cause of abdominal sepsis is a leakage of fecal

material from the intestinal lumen into the peritoneal cavity [10]. The leakage introduces gut bacteria, including *Enterobacteriaceae*, *Enterococcus* spp., *Streptococcus* spp., and *Staphylococcus* spp., into the sterile peritoneal environment. Another prospective study of 32 patients admitted to the ICU after the trauma and acute care surgery service similarly found a replacement of intestinal *Faecalibacterium* and *Ruminococcus* with the more pathogenic *Enterococcus* [11]. The site of infection is not usually in the gut, but the metabolic influence of the pathogens on the gut microbiota and host tends to be persistently overlooked. For example, microbes that flourished in the guts of elite athletes boosted the time that lab mice ran on a treadmill. These particular microbes seem to take lactate, pumped out by muscles during exercise, and turn it into a compound that may contribute to endurance [12].

In our preliminary study, we used gas chromatography-mass spectrometry (GC-MS) analysis of blood serum and feces simultaneously and at the same time analyzed the taxonomic composition of the gut microbiota using 16S rRNA gene-based metagenomic analysis in groups of patients with sepsis, n = 9, and healthy, n = 5. The sepsis was diagnosed according to the Sepsis 3 definition [7].

The taxonomic composition of the gut microbiota in a group at the phylum level as determined by the metagenomic analysis of feces is shown in **Figure 1**. The major four phyla of the human gut microbiota, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Actinobacteria*, were the predominant phyla in most patients. The composition of the gut microbiota was not stable in any of the patients, and dynamic changes were observed in all nine patients. At the same time, the absolute percentage of *Proteobacteria* in septic patients was several times higher than in healthy volunteers. This was confirmed at the family level. The *Enterobacteriaceae* family, which is a part of the *Proteobacteria*, was shown to represent the leading species among the top 10 in sepsis. However, clear understanding cannot be reached using only taxonomy since it allows to observe only a handful of processes taking place in the development of any infection (**Figure 1**).

As we have shown earlier, high levels of some aromatic microbial metabolites (AMMs) in serum are related to the severity and mortality of critically ill patients [13]. The sum of the level of eight most relevant metabolites, benzoic (BA), phenylpropionic (PhPA), phenyllactic (PhLA), p-hydroxyphenylbenzoic (p-HBA), p-hydroxyphenylacetic (p-HPhAA), p-hydroxyphenylpropionic (p-HPhPA), homovanillic (HVA), and p-hydroxyphenyllactic acids (p-HPhLA), in serum samples from septic patients was higher than in healthy people 3.7 (1.2–8.0) μM and 1.3 (1.0–1.6) μM, respectively ($p < 0.05$). In the septic group, the maximum values of the sum of these metabolites were more than 10 μM which is higher than in patients with lethal outcome. The differences in the AMM quality profiles of simultaneously serum and fecal samples (SFS) of patients with sepsis and healthy are presented in **Figure 2**. The results showed that the feces of healthy people abound with such metabolites, p-PhAA, p-HPhPA, and p-HPhLA, supporting data obtained by Jenner et al. [14]. At the same time, we observed prevalence of BA, PhLA, and p-PhAA in sepsis with a higher level of BA in the gut of non-survivors. Differences in the proportion of AMM in the blood compared to the intestine can be explained by the fact that most hydrophilic (p-HPhAA, p-HPhLA, and PhLA) metabolites are excreted by the kidneys, while lipophilic metabolites (BA, PhAA, and PhPA) are absorbed by cells of tissue barriers (intestinal wall, lymphoid tissue, liver, vascular endothelium, etc.).

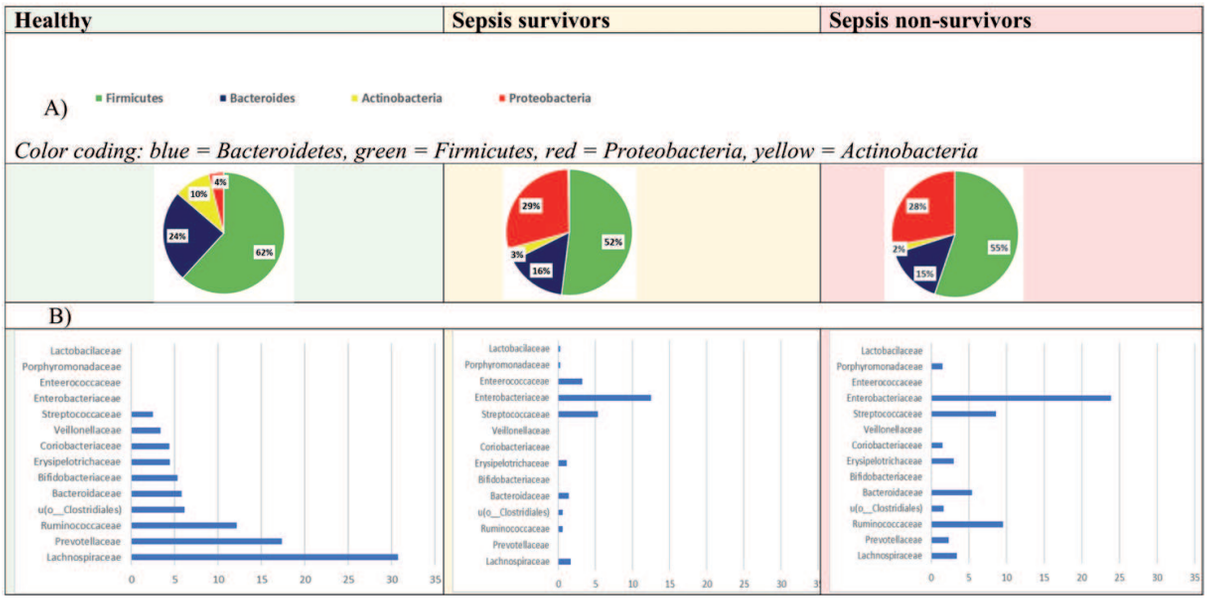

Figure 1. Taxonomic composition of the gut microbiota by metagenomic analysis. Comparison the taxonomic composition of the gut microbiota: (a) at the major phylum and (b) by top 10 families.

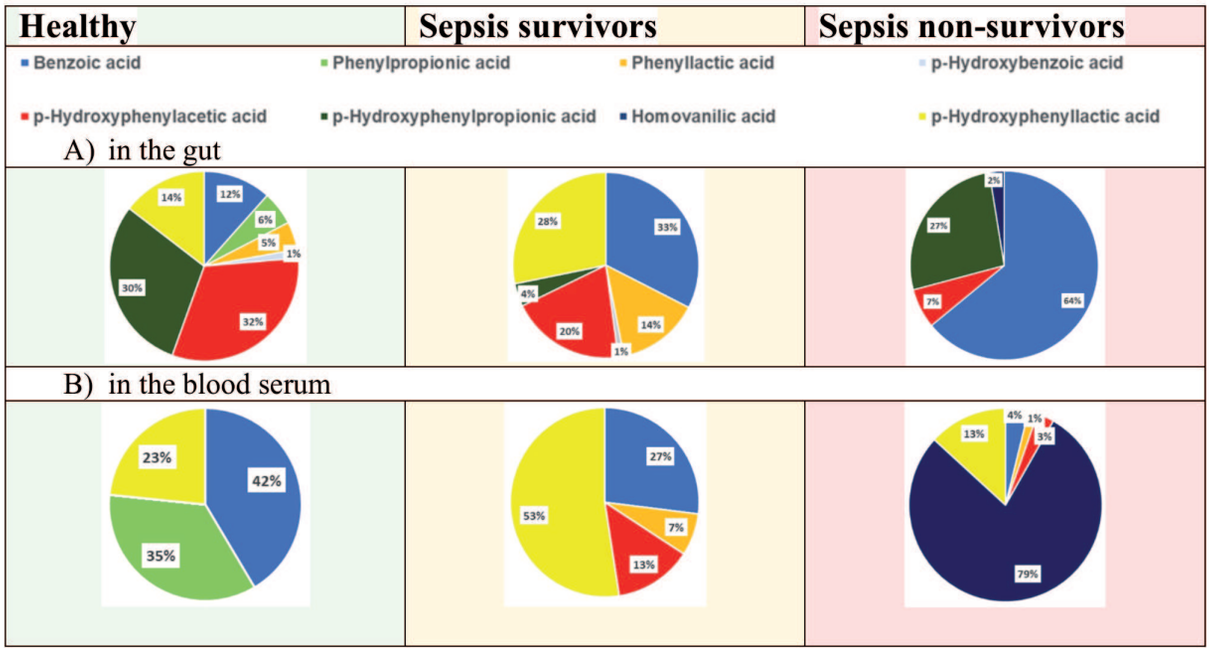

Figure 2. Metabolic profile of aromatic metabolites in: (A) the gut and (B) the blood serum. The data are presented by median of the proportion of each acid among all AMMs.

In particular, serum samples of healthy people are characterized by a predominance of BA and PhPA, while hydrophilic AMMs are detected in sepsis with the appearance of high levels of HVA in the serum of non-survivors. BA is a product of the synthesis of bacteria, plants, and fungi, but a significant content is formed as a result of biodegradation of phenylalanine.

Experimental study of the proximal part of the gastrointestinal tract showed that BA had a bacteriostatic and bactericidal dose-dependent effect on coliform and lactic acid bacteria [15].

On the one hand, it is important to emphasize that the dysfunction of the microbiota is manifested by excessive production of certain microbial metabolites as a reflection of the high microbial load with pathological colonization by bacteria involved in the development of sepsis. On the other hand, microbiota function, which is very important for host homeostasis, such as microbial biodegradation of an excess of endogenous biologically active compounds, due to a decrease in biodiversity in the intestine, primarily a deficiency of indigenous anaerobes, is disturbed [16]. The altered profile of aromatic metabolites in the blood may be an integral indicator reflecting these dramatic disturbances and possibly other functions of the "invisible organ."

3. The gut microbial metabolites in the pathogenesis of sepsis

It was shown that in vitro some sepsis-associated AMM in clinically significant concentrations can inhibit the phagocytic activity of neutrophils [17]; cause mitochondrial dysfunction [18]; influence on platelet aggregation [19]; reduce tyrosine hydroxylase activity, thus limiting the synthesis of catecholamines; and participate in the pathogenesis of septic shock [20]. Numerous data obtained in vitro allow us to hypothesize that AMM acts as signaling molecules (**Figure 3**).

It is impossible to exclude the presence of common signaling pathways, cell receptors, transmembrane transporters, and other mechanisms of humans and bacteria, as well as the direct participation of microbial metabolites in the pathogenesis of sepsis. Thus, today, we should not confine ourselves to studying eukaryotic cells while searching for new molecular mechanisms of sepsis-associated organ failure and septic shock [20]. We should consider

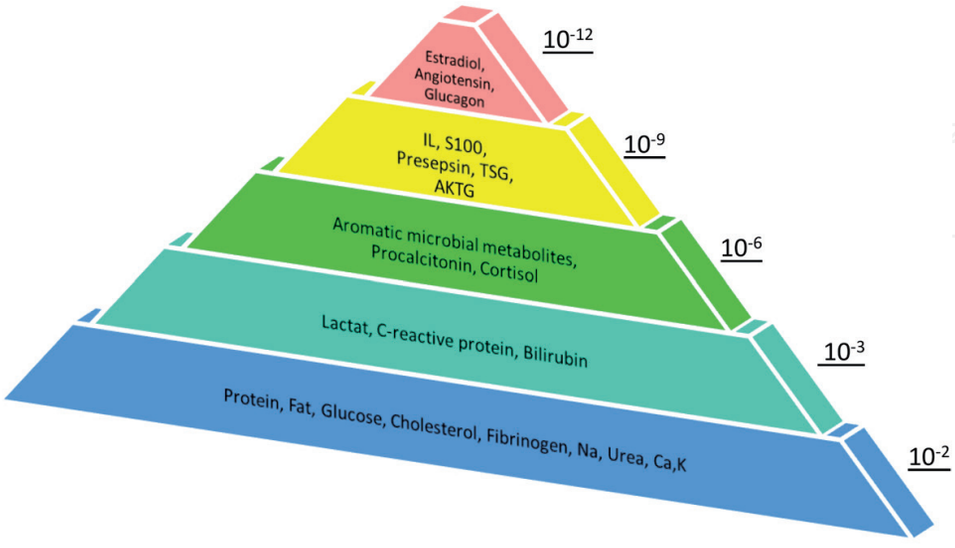

Figure 3. Schematic representation of levels of some biochemical parameters, metabolites, and hormones in blood serum in comparison.

and simulate experimental changes in the internal environment of a person that occur with a radical "restructuring" of the microbiome in seriously ill patients. This approach opens new prospects for an objective monitoring of diseases, carrying out an assessment of the integral metabolic profile on common metabolites (particularly aromatic) within a given time, and will provide new targets for therapeutic effects in the future.

4. Microbiome-oriented therapy: how to keep balance?

In sepsis, disturbances of physiological parameters caused directly by patient's conditions and multiple treatment-induced factors might have powerful impact on the gut microbiome. Finding a therapy aimed at restoring the balance between "beneficial" and "harmful" microorganisms is highly relevant. At present, there are several possible approaches (**Table 1**):

- Increase the "beneficial" microorganisms using pro-, pre-, and/or metabiotics.
- Use a combination of probiotics and prebiotics known as symbiotics.
- Improve the composition by transplantation of fecal microbiota transplantation (FMT).
- Suppress "harmful" microorganisms, and create favorable conditions for recovery of one's own "beneficial" microorganisms using selective antibacterial drugs (similar selective digestive decontamination).

The undoubtful effectiveness of probiotics for correction of functional disorders of the gastrointestinal tract has been widely accepted. A randomized placebo-controlled study on 4556 healthy newborns in India proved that oral probiotics *Lactobacillus plantarum* combined with fructo-oligosaccharides during the first postnatal week helped reduce sepsis incidence during the first 60 days of life [21]. A randomized, double-blind, placebo-controlled, experimental study of changes in the microbiome and intestinal barrier in early sepsis showed that probiotic intervention successfully modulates the microbiome and is therefore a promising tool for early intervention in sepsis [22]. At the same time, there are no recommendations for the use of probiotics in ICU yet. Present studies differ due to the diseases in patients, the microorganism strains used, and the prescribed dosage of probiotics. There is no consensus concerning the beginning and duration of treatment. As for today, the largest study of efficacy of probiotics and symbiotics in ICU patients was carried out by Manzanares et al. The sample of over 2700 patients demonstrated that the use of probiotics for microbiota recovery reduced incidence of infectious complications (specifically, ventilation-associated pneumonias); it was possible to reduce the use of antibiotics without increasing mortality or length of stay in ICU [23].

In another study, the use of symbiotics as an adjuvant therapy in surgical patients reduced incidence of such postoperative complications as wound infection [24]. One of the reasons for doubts concerning expediency of applying probiotics in ICU is intestinal barrier failure in critically ill patients. The translocation of bacteria to systemic blood flow and lymph is known to promote a complex chain of events leading to multiple organ failure [34]. On this

	Study	Population	Type of intervention	Results
Probiotics/symbiotics				
☺	Panigrahi et al. [21]	4556 healthy newborns	*Lactobacillus plantarum*	Reduction in the incidence of sepsis during the first 60 days of life
☺	Stadlbauer et al. [22]	15 patients with early sepsis	The multispecies probiotic in a dose of 10^9 daily	Probiotic intervention successfully modulates the microbiome
☺	Manzanares et al. [23]	Meta-analysis of 30 trials that enrolled 2972 critically ill patients	Different types of probiotic therapy	Probiotics were associated with a significant reduction in infections (risk ratio 0.80, 95% confidence interval (CI) 0.68, 0.95, P = 0.009; heterogeneity I2 = 36%, P = 0.09)
☺	Kasatpibal et al. [24]	Meta-analysis of 31 articles that enrolled 2952 surgical patients	Different types of probiotic, prebiotic and symbiotic therapy	Symbiotic therapy was the best regimen in reducing surgical site infection (SSI) (RR = 0.28; 95% CI, 0.12–0.64)
☺	Besselink et al. [25]	298 patients with predicted severe acute pancreatitis	4 species of lactic bacterial (*L. acidophilus*, *L. casei*, *L. salivarius*, *L. lactis*), and 2 species of bifid bacteria (*B. bifidum*, *B. lactis*) in a dose of 10^{10} daily	Probiotic prophylaxis is associated with an increased risk of mortality and higher rate of infectious complications
FMT				
☺	Han et al. [26]	Review of management of *Clostridium difficile* infection (CDI) with a focus on FMT	FMT	The potential effective therapy but not enough data in the ICU patients
☺	Moayyedi et al. [27]	Meta-analysis of 5 trials that enrolled 284 patients with CDI	FMT (including autologous FMT)	FMT was statistically significantly more effective (RR, 0.41; 95% CI, 0.22–0.74; NNT, 3; 95% CI, 2–7) than vancomycin or placebo
☺	McClave et al. [28]	Review of clinical use of fecal microbial transplantation in critical illness	FMT	An attractive option to mitigate multiple organ dysfunction in the ICU
☺	FDA [29]	Two immunocompromised patients	FMT	The development of a severe infection and one death from fecal transplants containing drug-resistant bacteria

	Study	Population	Type of intervention	Results
SDD				
☺	Price et al. [30]	Meta-analysis of 29 articles that enrolled patients in general intensive care units	SDD	Favorable effect on mortality, with a direct evidence odds ratio of 0.73 (95% confidence interval 0.64 to 0.84)
☺	Buelow et al. [31]	10 ICU patients	SDD	The limited risks for antibiotic resistance
				SDD related
☺	Webster et al. [32]	Meta-analysis of 37 trials (involving more than 7000 patients)	SDD	SDD reduces ventilator-associated pneumonia (odds ratio (OR) = 0.28; 95% confidence interval (CI) = 0.20–0.38) and mortality (OR = 0.73; CI = 0.64–0.84)
Antimicrobial therapy under the control of the metabolic activity of the gut microbiota				
☺	Beloborodova and Sarshor [33]	56 patients with pneumonia or abdominal infection	Enteral correction of the metabolic activity of the gut microbiota	The downward trend of mortality by 11%

Table 1. Generalized data on the possible current use of microbiome therapy.

basis, the use of live bioculture drugs (probiotics) in critically ill patients looks far from harmless and even dangerous. Possible, a NGS-based approach for the detection of bacteremia in patients with sepsis, which has shown promising results, will be a key step in the clinical use of NGS in this indication [35]. In randomized double-blind placebo-controlled independent study on severe acute pancreatitis patients (n = 298)—Probiotics in Pancreatitis Trial (PROPATRIA)—1 group (n = 153), for prophylaxis of suppurative complications received a biomedicine containing 4 species of lactic bacterial (*L. acidophilus*, *L. casei*, *L. salivarius*, *L. lactis*) and 2 species of bifid bacteria (*B. bifidum*, *B. lactis*) in a dose of 10^{10} daily, while the control group (n = 145) received placebo. The results disappointed the researches: in the group of patients who received probiotics, more severe course of the disease was recorded, necrotizing pancreatitis developed more frequently, secondary bacteremia and other infectious complications occurred, multiple organ failure developed reliably more frequently, and mortality was higher (p = 0.01). The authors of the study were unable to provide convincing explanations but expressed their doubts concerning reasonability for use of probiotics in critically ill patients [25].

In our opinion, the use of live microbial cultures of lactic acid bacteria might have aggravated metabolic disturbances and led to adverse consequences in initially severe patients, in particular, because of excessive production of PhLA and p-HPhLA which are typical metabolites of bifido- and lactic bacteria [36, 37]. A group of authors who used probiotics with positive effect in short bowel syndrome patients have reached similar conclusions, namely, the importance of metabolic status evaluation. The colleagues associated high mortality in PROPATRIA

study with lethal combination of proteolytic enzymes of pancreas and high level of lactic acid caused by bacterial fermentation of carbohydrates as a key factor related to intake of probiotics. Nevertheless, authors suggest that a probiotic therapy may not be counterindicated for the prevention of secondary infections associated with acute pancreatitis, provided that future clinical studies start probiotic therapy early as possible and prevent bacterial overgrowth not only of patient's own intestinal flora but also the dose of probiotic bacteria [38].

An alternative to probiotics, "smart" direction, is infusion of liquid filtrate of feces from healthy fecal microbiota transplantation. The potential advantage of this method is enlargement of microbial biodiversity and the presence of biologically active substances and metabolites, which might assist a longer effect of microbiota recovery [39]. This procedure has been successfully used for treating the severe infection caused by *Clostridium difficile* in more than 1000 patients [26]. The recent meta-analysis (n = 284) has shown that FMT is significantly more effective in the treatment of such patients compared to the control group in spite of heterogeneity of groups due to the study sites (Europe vs. North America) and method of administration [27]. However, the current experience of FMT application in ICU is limited just to a few patients described only in sporadic publications [28]. The limited quantity of data, absence of objective criteria for efficacy evaluation, and insufficient knowledge of microbiota composition dynamics and its metabolic activity preclude wide application of this method in such vulnerable group of patients. The FDA does not currently approve of any use of fecal transplants. Two patients contracted severe infections, and one of them died, from fecal transplants that contained drug-resistant bacteria [29]. Putting it in another way, given the knowledge and risks, the use of FMT in critically ill patients can be compared to the first blood transfusion before the opening of the ABO system [19].

We assume that the main efforts in fighting infection should be directed to decrease microbial metabolic activity. Considering that the intestine is the main reservoir of bacteria and therefore the main source of bacterial metabolites, it seems appropriate to correct the activity of intestinal microbiota in patient with infection. Enteral correction of the metabolic activity of intestinal microbiota contributes to the improvement of the patients' state [33].

Selective digestive decontamination (SDD) is often considered a prophylactic mode of antibiotic therapy allowing targeted prevention of bowel colonization by "pathogenic" microorganisms. The effect is achieved thanks to the selective impact on potentially pathogenic aerobic and facultative aerobic bacteria by means of enteral administration of antibacterial drugs that do not suppress anaerobic microorganisms, thus creating conditions for recovery of microbiota balance and assisting its functioning even in the unfavorable environment in ICU. Currently, numerous clinical studies and meta-analyses have shown that SDD helps prevent hospital infection in ICU and reduce mortality [30]. Wide implementation of SDD was restricted, inter alia, because of fears of increasing resistance of nosocomial microorganisms to antibiotics [31]; however, convincing data have been obtained confirming the absence of resistant bacterial growth at the background of selective decolonization. A number of major investigations are currently underway, and their authors are expected to give shortly new clinical recommendations concerning the use of this method in ICU [32]. The pronounced clinical effect may be associated with a change in the profile of microbial metabolites, which requires additional research.

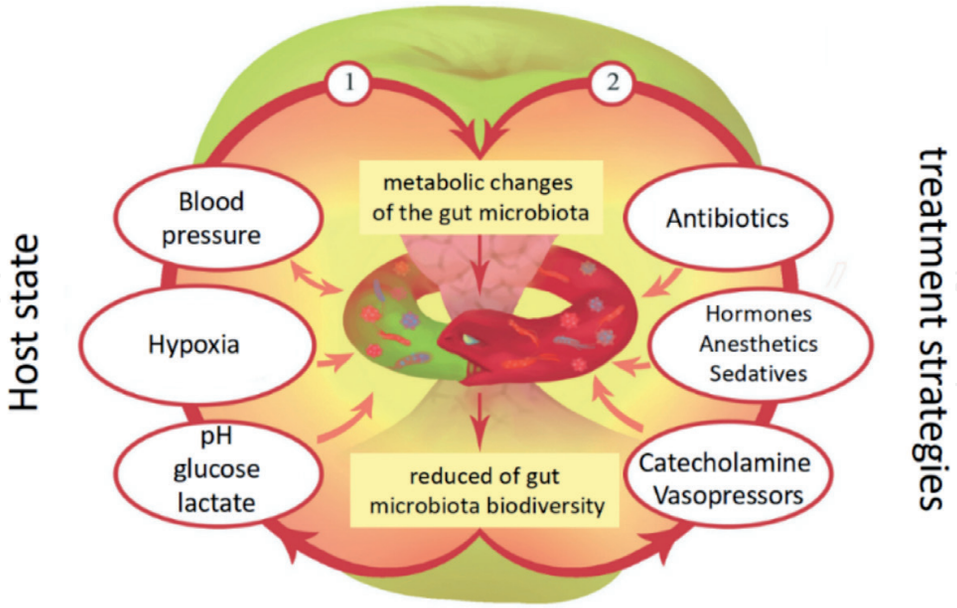

Figure 4. Factors affecting the metabolism of microbiota in ICU [41].

As shown above, the "harmful/beneficial" gut bacteria disbalance is frequently associated with nosocomial pathogens and adverse outcome. The influence of negative factors related to changed internal environment of the macroorganism, and rather aggressive therapy leads to a drastic change in the species diversity of microbiota [40] and, as a consequence, a disturbance of functional activity of microbial community and a development of the maximal disorders that may cause irreversible breakdowns of homeostasis and host body death. A "vicious circle" is created: disturbance of gut microbiome function in critically ill patients leads to overproduction of certain microbial metabolites, which, in turn, have pathological impact on macroorganism's organs and systems (**Figure 4**).

Two potential points of effect in sepsis treatment can be identified as:

1. Host state: prognosing negative dynamics of homeostasis indices as critical condition progresses and maximally sparing regimens of antimicrobial therapy taking into account the important role of microbiome
2. Treatment strategies: suppression of overgrowth and targeted correction of bacterial metabolism [41]

5. Conclusion

So, are the microbiota-oriented diagnostics and therapy in sepsis a utopia or necessity? In real clinical practice, it is not yet possible to provide real-time monitoring of the microbiome, due to such diagnostics being time-consuming, expensive, complex, and insufficiently studied. Previous works have noted that the gut is a "motor of multiple organ failure and sepsis" [42], and its

underestimation earned it a name of "forgotten organ." In the past decades, the number of studies of microbiota in various diseases, including sepsis, has increased drastically and is likely to keep rising. Now it is clear that the "forgotten organ" is a reservoir of pathogens and possibly of genes associated with antibiotic resistance, as well as a marker of disease severity and outcome. Therapy aimed at restoring microbiota equilibrium rather than blindly prescribing broad-spectrum antibiotics may be the best choice. Understanding the metabolic language of microorganisms will serve as a catalyst for the development of new strategies, which will be especially important in the era of antibiotic resistance. New, culturally independent technologies allowing a fast accurate and comprehensive assessment of microbiome will be adapted in the coming years for practical use and wide application. Characterization of changes in ICU patient's microbiome will enable advancement in the development of diagnostic and therapeutic interventions based on changes not only in the microbiota's composition but also in its metabolic profile as well.

6. Methods

We used gas chromatography-mass spectrometry (GC-MS) method to quantify metabolites in human serum from septic patients and healthy volunteers. For taxonomic identification of samples, Ion 16S Metagenomics Kits, Ion Reporter metagenomic workflow solution, and Ion Torrent sequencing systems were used. Clinical and laboratory data and APACHE II and SOFA scores in patients were matched. Data were compared by Mann-Whitney U test; p-values less than 0.05 were considered significant.

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References

[1] Wolff NS, Hugenholtz F, Wiersinga WJ. The emerging role of the microbiota in the ICU. Critical Care. 2018;**22**(1):78. DOI: 10.1186/s13054-018-1999-8

[2] Haak BW, Wiersinga WJ. The role of the gut microbiota in sepsis. The Lancet Gastroenterology and Hepatology. 2017;**2**:135-143. DOI: 10.1016/S2468-1253(16)30119-4

[3] Beloborodova NV, Grechko AV, Olenin AY. Metabolomic discovery of microbiota dysfunction as the cause of pathology. IntechOpen. [Online First] 26 June 2019. DOI:

10.5772/intechopen.87176. Available from: https://www.intechopen.com/online-first/metabolomic-discovery-of-microbiota-dysfunction-as-the-cause-of-pathology

[4] Schmidt K, Mwaigwisya S, Crossman LC, Doumith M, Munroe D, Pires C, et al. Identification of bacterial pathogens and antimicrobial resistance directly from clinical urines by nanopore-based metagenomic sequencing. The Journal of Antimicrobial Chemotherapy. 2017;**72**(1):104-114. DOI: 10.1093/jac/dkw397

[5] Thomas AM, Segata N. Multiple levels of the unknown in microbiome research. BMC Biology. 2019;**17**(1):48. DOI: 10.1186/s12915-019-0667-z

[6] Angus DC, van der Poll T. Severe sepsis and septic shock. The New England Journal of Medicine. 2013;**369**(9):840-851. DOI: 10.1056/NEJMra1208623

[7] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). Journal of the American Medical Association. 2016;**315**(8):801-810. DOI: 10.1001/jama.2016.0287

[8] Dickson RP. The lung microbiome and ARDS. It is time to broaden the model. American Journal of Respiratory and Critical Care Medicine. 2018;**197**(5):549-551. DOI: 10.1164/rccm.201710-2096ED

[9] Ramsey M, Hartke A, Huycke M. The physiology and metabolism of enterococci. In: Gilmore MS, Clewell DB, Ike Y, Shankar N, editors. Enterococci: From Commensals to Leading Causes of Drug Resistant Infection [Internet]. Boston: Massachusetts Eye and Ear Infirmary; 2014

[10] Weledji EP, Ngowe MN. The challenge of intra-abdominal sepsis. International Journal of Surgery. 2013;**11**(4):290-295. DOI: 10.1016/j.ijsu.2013.02.021

[11] Yeh A, Rogers MB, Firek B, Neal MD, Zuckerbraun BS, Morowitz MJ. Dysbiosis across multiple body sites in critically ill adult surgical patients. Shock. 2016;**46**(6):649-654. DOI: 10.1097/SHK.0000000000000691

[12] Scheiman J, Luber JM, Chavkin TA, MacDonald T, Tung A, Pham LD, et al. Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism. Nature Medicine. 2019;**25**(7):1104-1109. DOI: 10.1038/s41591-019-0485-4

[13] Beloborodova NV. Chapter 1. Interaction of host-microbial metabolism in sepsis. In: Kumar V editor. Sepsis. Croatia, Rijeka: InTech; 2017. p. 3-19. DOI: 10.5772/68046. Print ISBN 978-953-51-3395-7, 158 pages. DOI: 10.5772/65611. Available from: https://www.intechopen.com/books/sepsis

[14] Jenner AM, Rafter J, Halliwell B. Human fecal water content of phenolics: The extent of colonic exposure to aromatic compounds. Free Radical Biology and Medicine. 2005;**38**(6):763-772. DOI: 10.1016/j.freeradbiomed.2004.11.020

[15] Knarreborg A, Miquel N, Granli T, Jensen BB. Establishment and application of an in vitro methodology to study the effects of organic acids on coliform and lactic acid

bacteria in the proximal part of the gastrointestinal tract of piglets. Animal Feed Science and Technology. 2002;**99**(1):131-140. DOI: 10.1016/S0377-8401(02)00069-X

[16] Beloborodova NV. Sepsis—Metabolomic Approach. Moscow: Meditsin-skoe Informatsionnoe Agentstvo; 2018. 272p. ISBN: 978-5-9986-0350-1. [In Russ.]

[17] Beloborodova NV. Integration of metabolism in man and his microbiome in critical conditions. General Reanimatology. 2012;**8**(4):42-54. DOI: 10.15360/1813-9779-2012-4-42. [In Russ., In Engl.]

[18] Fedotcheva NI, Kazakov RE, Kondrashova MN, Beloborodova NV. Toxic effects of microbial phenolic acids on the functions of mitochondria. Toxicology Letters. 2008;**180**(3):182-188. DOI: 10.1016/j.toxlet.2008.06.861

[19] Chernevskaya E, Beloborodova NV, Bulychev A. Potential contribution of aromatic microbial metabolites to platelet aggregation disturbance. Intensive Care Medicine Experimental. 2018;**6**(Suppl 1):P41. DOI: 10.1186/s40635-018-0196-z

[20] Beloborodova NV, Sarshor YN, Bedova AY, Chernevskaya EA, Pautova AK. Involvement of aromatic metabolites in the pathogenesis of septic shock. Shock. 2018;**50**:273. DOI: 10.1097/shk.0000000000001064

[21] Panigrahi P, Chandel DS, Hansen NI, Sharma N, Kandefer S, Parida S, et al. Neonatal sepsis in rural India: Timing, microbiology and antibiotic resistance in a population-based prospective study in the community setting. Journal of Perinatology. 2017;**37**(8):911-921. DOI: 10.1038/jp.2017.67

[22] Stadlbauer V, Horvath A, Komarova I, Schmerboeck B, Feldbacher N, Klymiuk I, et al. Dysbiosis in early sepsis can be modulated by a multispecies probiotic: A randomised controlled pilot trial. Beneficial Microbes. 2019;**10**(3):265-278. DOI: 10.3920/BM2018.0067

[23] Manzanares W, Lemieux M, Langlois PL, Wischmeyer PE. Probiotic and synbiotic therapy in critical illness: A systematic review and meta-analysis. Critical Care. 2016;**19**:262. DOI: 10.1186/s13054-016-1434-y. PMID:27538711

[24] Kasatpibal N, Whitney JD, Saokaew S, Kengkla K, Heitkemper MM, Apisarnthanarak A. Effectiveness of probiotic, prebiotic, and synbiotic therapies in reducing postoperative complications: A systematic review and network meta-analysis. Clinical Infectious Diseases. 2017;**64**(suppl_2):S153-S160. DOI: 10.1093/cid/cix114

[25] Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Dutch acute pancreatitis study group. Probiotic prophylaxis in predicted severe acute pancreatitis: A randomised, double-blind, placebo-controlled trial. Lancet. 2008;**371**(9613):651-659. DOI: 10.1016/S0140-6736(08)60207-X

[26] Han S, Shannahan S, Pellish R. Fecal microbiota transplant: Treatment options for *Clostridium difficile* infection in the intensive care unit. Journal of Intensive Care Medicine. 2015;**31**(9):577-586. DOI: 10.1177/0885066615594344

[27] Moayyedi P, Yuan Y, Baharith H, Ford AC. Faecal microbiota transplantation for *Clostridium difficile*-associated diarrhoea: A systematic review of randomised controlled trials. The Medical Journal of Australia. 2017;**207**(4):166-172. DOI: 10.5694/mja17.00295

[28] McClave SA, Patel J, Bhutiani N. Should fecal microbial transplantation be used in the ICU? Current Opinion in Critical Care. 2018;**24**(2):105-111. DOI: 10.1097/MCC.0000000000000489

[29] Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms. FDA.GOV. 13 June 2019. Available from: https://www.fda.gov/news-events/fda-brief/fda-brief-fda-warns-about-potential-risk-serious-infections-caused-multi-drug-resistant-organisms

[30] Price R, MacLennan G, Glen J, SuDDICU Collaboration. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. BMJ. 2014;**348**:g2197. DOI: 10.1136/bmj.g2197

[31] Buelow E, Bello González TDJ, Fuentes S, de Steenhuijsen Piters WAA, Lahti L, Bayjanov JR, et al. Comparative gut microbiota and resistome profiling of intensive care patients receiving selective digestive tract decontamination and healthy subjects. Microbiome. 2017;**5**(1):88. DOI: 10.1186/s40168-017-0309-z

[32] Webster F, Weijer C, Todd L, Grimshaw JM, Marshall AP, Cook D, et al. The ethics of future trials: Qualitative analysis of physicians' decision making. Trials. 2016;**17**:12. DOI: 10.1186/s13063-015-1137-8

[33] Beloborodova N, Sarshor Y. The first experience of targeted antibiotics for the regulation of the metabolic activity of the gut microbiota (MAGM) in critically ill patients with pneumonia or abdominal infection. Intensive Care Medicine Experimental. 2018;**6**(Suppl 2):0399. DOI: 10.1186/s40635-018-0201-6

[34] Klingensmith NJ, Coopersmith CM. The gut as the motor of multiple organ dysfunction in critical illness. Critical Care Clinics. 2016;**32**(2):203-212. DOI: 10.1016/j.ccc.2015.11.004

[35] Brenner T, Decker SO, Grumaz S, Stevens P, Bruckner T, Schmoch T, et al. Next-generation sequencing diagnostics of bacteremia in sepsis (Next GeneSiS-Trial): Study protocol of a prospective, observational, noninterventional, multicenter, clinical trial. Medicine (Baltimore). 2018;**97**(6):e9868. DOI: 10.1097/MD.0000000000009868

[36] Beloborodova NV, Khodakova AS, Bairamov IT, Olenin AY. Microbial origin of phenylcarboxylic acids in the human body. Biochemistry (Moscow). 2009;**74**(12):1350-1355

[37] Beloborodova NV, Baĭramov IT, Olenin AI, Fedotcheva NI. Exometabolites of some anaerobic microorganisms of human microflora. Biomeditsinskaya Khimiya. 2011;**57**(1): 95-105. Russian

[38] Bongaerts GP, Severijnen RS. A reassessment of the PROPATRIA study and its implications for probiotic therapy. Nature Biotechnology. 2016;**34**(1):55-63. DOI: 10.1038/nbt.3436

[39] van Nood E, Speelman P, Nieuwdorp M, Keller J. Fecal microbiota transplantation: Facts and controversies. Current Opinion in Gastroenterology. 2014;**30**(1):34-39. DOI: 10.1097/MOG.0000000000000024

[40] Dickson RP. The microbiome and critical illness. The Lancet Respiratory Medicine. 2016;**4**(1):59-72. DOI: 10.1016/S2213-2600(15)00427-0

[41] Chernevskaya E, Beloborodova N. Gut microbiome in critical illness (review). General Reanimatology. 2018;**14**:96. DOI: 10.15360/1813-9779-2018-5-96-119

[42] Marshall JC. Gastrointestinal flora and its alterations in critical illness. Current Opinion in Clinical Nutrition and Metabolic Care. 1999;**2**(5):405-411. DOI: 10.1097/00075197-199909000-00009

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