CHAPTER 13

CURRENT CONCEPTS OF METABOLIC HEALTH: PRINCIPLES OF SCREENING AND CLINICAL DIAGNOSIS

Kalinichenko S. V., Kordon T. I., Dubinina N. V.
DOI https://doi.org/10.30525/978-9934-26-727-7-13

INTRODUCTION

The concept of the enteric nervous system (ENS) was introduced by John Newport Langley in 1921 as the third division of the autonomic nervous system. Later, following the pioneering work of Michael Gershon, the ENS became widely recognized as the "second brain" or the "brain of the gut"[1]. In contemporary neurogastroenterology, these concepts have evolved into the broader framework of the gut-brain axis, which describes the complex bidirectional communication network linking the gastrointestinal tract and the central nervous system[2]. According to the European Association for the Study of the Liver (EASL), disturbances in the composition of the intestinal microbiota (gut dysbiosis) may contribute to reduced serotonin production, as approximately 90 % of the body's serotonin is synthesized by enterochromaffin cells in the intestine. Alterations in serotonin homeostasis have been associated with anxiety, irritability, depression, and impaired psychological well-being[3].

The brain and the enteric nervous system share numerous structural and functional characteristics. Enteric glial cells closely resemble astrocytes of the central nervous system, while both the brain and the intestinal microbiota produce a wide range of neuroactive molecules, neurotransmitters, and regulatory peptides[4]. Furthermore, inflammatory processes may compromise both the intestinal epithelial barrier and the blood-brain barrier, thereby

[1] Brunet J.-F. Gaskell, Langley, and the "para-sympathetic" idea // *eLife*. 2025. Vol. 14. DOI: 10.7554/eLife.104826.

[2] Zhang J., Fallon M. B. Hepatopulmonary syndrome: update on pathogenesis and clinical features // *Nature Reviews Gastroenterology & Hepatology*. 2012. Vol. 9, № 9. P. 539–549. DOI: 10.1038/nrgastro.2012.123.

[3] Appleton J. The Gut-Brain Axis: Influence of Microbiota on Mood and Mental Health // *Integrative Medicine (Encinitas)*. 2018. Vol. 17, № 4. P. 28–32.

[4] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis // *Journal of Hepatology*. 2017. Vol. 67, № 1. P. 145–172. DOI: 10.1016/j.jhep.2017.03.022

facilitating bidirectional communication between peripheral and central immune responses[5]. Innate immune receptors, particularly Toll-like receptors (TLRs), play an essential protective role by recognizing microbial and viral pathogen-associated molecular patterns and initiating appropriate immune responses[6]. Growing evidence demonstrates that signals originating from the gastrointestinal tract substantially influence emotions, mood, cognition, and behavior. During early life, the intestinal microbiota plays a critical role in neurodevelopment and cognitive maturation[7]. Alterations in microbial composition have been associated with numerous neurological and psychiatric disorders, including autism spectrum disorders, schizophrenia, anxiety disorders, depression, multiple sclerosis, Alzheimer's disease, and Parkinson's disease[8].

Stress represents one of the principal factors disrupting communication along the gut-brain axis[9]. During acute stress, activation of the hypothalamic-pituitary-adrenal (HPA) axis stimulates the sequential release of corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), and glucocorticoids, primarily cortisol3. Chronic stress, in contrast, promotes persistent low-grade inflammation characterized by increased circulating concentrations of C-reactive protein, interleukin-6, and other pro-inflammatory cytokines, together with activation of the nuclear factor kappa B (NF-κB) signaling pathway[10]. Collectively, these findings demonstrate that multiple interacting factors contribute to disruption of the gut-brain axis and may participate in the development of central nervous system disorders. A comprehensive understanding of these mechanisms is therefore essential for developing novel strategies aimed at restoring the functional interactions between the brain and the intestinal microbiota.

---

5 Clapp M., Aurora N., Herrera L., Bhatia M., Wilen E., Wakefield S. Gut microbiota's effect on mental health: The gut-brain axis // *Clinical Practice*. 2017. Vol. 7, № 4. Article 987. DOI: 10.4081/cp.2017.987.

6 Madison A., Kiecolt-Glaser J. K. Stress, depression, diet, and the gut microbiota: human-bacteria interactions at the core of psychoneuroimmunology and nutrition // *Current Opinion in Behavioral Sciences*. 2019. Vol. 28. P. 105–110. DOI: 10.1016/j.cobeha.2019.01.011.

7 Ronan V., Yeasin R., Claud E. C. Childhood development and the microbiome: the intestinal microbiota in maintenance of health and development of disease during childhood development // *Gastroenterology*. 2021. Vol. 160, № 2. P. 495–506. DOI: 10.1053/j.gastro.2020.08.065.

8 Irum N., Afzal T., Faraz M. H., Aslam Z., Rasheed F. The role of gut microbiota in depression: an analysis of the gut-brain axis // *Frontiers in Behavioral Neuroscience*. 2023. Vol. 17. Article 1185522. DOI: 10.3389/fnbeh.2023.1185522.

9 Wang Q., Yang Q., Liu X. The microbiota-gut-brain axis and neurodevelopmental disorders // *Protein & Cell*. 2023. Vol. 14, № 10. P. 762–775. DOI: 10.1093/procel/pwad026.

10 Liu Z., Lei M., Bai Y. Chronic stress mediates inflammatory cytokines alterations and its role in tumorigenesis // *Journal of Inflammation Research*. 2025. Vol. 18. P. 1067–1090. DOI: 10.2147/JIR.S485159.

1. Gut microbiota and human health: current state of knowledge

The gut microbiota is currently recognized as one of the key regulators of the interactions among the digestive, immune, endocrine, and nervous systems. The collective bidirectional communication among these systems is described by the concept of the gut-brain axis, within which intestinal microorganisms can influence neurochemical processes, behavior, emotional state, and the risk of developing psychiatric and neurological disorders[11]. At the same time, the brain, through stress-related, neuroendocrine, and autonomic mechanisms, also modulates the composition and functional activity of the gut microbiota[12]. Contemporary scientific evidence has accumulated demonstrating the involvement of the gut microbiota in the pathogenesis of depression, anxiety disorders, post-traumatic stress disorder, as well as several neurodegenerative and inflammatory diseases. Nevertheless, this field remains highly complex and multifactorial, and many of the underlying mechanisms still require further elucidation.

The gut-brain axis is a complex communication network involving the central nervous system, the autonomic nervous system, the enteric nervous system, the immune system, the hypothalamic-pituitary-adrenal (HPA) axis, and the gut microbiota[12]. Its function is mediated through neuronal, humoral, immune, and metabolic signaling pathways that coordinate both local intestinal processes and central mechanisms regulating mood, stress responses, and behavior[13]. One of the principal pathways of communication between the gut and the brain is the vagus nerve. It mediates the rapid transmission of sensory information from the gastrointestinal tract to the central nervous system and is also involved in the reciprocal regulation of intestinal motility, secretion, and inflammatory responses[14]. Recent studies have demonstrated that enteroendocrine cells and the so-called neuropod cells, which are capable of converting chemical signals originating from the intestinal lumen into neuronal impulses, play a particularly important role in this communication. Thus, the intestine should be regarded not only as a digestive organ but also as a highly specialized sensory platform directly involved in neural regulation.

---

[11] Rusch J. A., Layden B. T., Dugas L. R. Signalling cognition: the gut microbiota and hypothalamic-pituitary-adrenal axis // *Frontiers in Endocrinology*. 2023. Vol. 14. Article 1130689. DOI: 10.3389/fendo.2023.1130689.

[12] Rutsch A., Kantsjö J. B., Ronchi F. The Gut-Brain Axis: How Microbiota and Host Inflammasome Influence Brain Physiology and Pathology // *Frontiers in Immunology*. 2020. Vol. 11. Article 604179. DOI: 10.3389/fimmu.2020.604179.

[13] Dockray G. J. Enteroendocrine cell signalling via the vagus nerve // *Current Opinion in Pharmacology*. 2013. Vol. 13, № 6. P. 954–958. DOI: 10.1016/j.coph.2013.09.007.

[14] Tian P., Yang W., Guo X., Wang T., Tan S., Sun R. et al. Early life gut microbiota sustains liver-resident natural killer cells maturation via the butyrate–IL-18 axis // *Nature Communications*. 2023. Vol. 14. Article 1710. DOI: 10.1038/s41467-023-37419-7.

In addition to neural pathways, microbial metabolites play a pivotal role in the functioning of the gut-brain axis. These include short-chain fatty acids, tryptophan-derived metabolites, bile acids, and other compounds involved in the regulation of neurotransmitter synthesis and maintenance of intestinal barrier integrity[15]. Through these bioactive molecules, the gut microbiota is capable of modulating neuroinflammation, intestinal barrier permeability, immune cell activity, and even serotonin biosynthesis[16].

The gut microbiota plays a fundamental role in the education and maturation of the immune system, particularly during the early stages of life. It contributes to the establishment of immune tolerance toward commensal microorganisms, regulates the maturation of both innate and adaptive immune cells, and maintains the balance between pro-inflammatory and anti-inflammatory immune responses[17]. Disruption of this balance may promote the development of chronic inflammation, autoimmune diseases, and, potentially, psychiatric disorders[18]. The immune system represents one of the principal mediators through which the gut microbiota influences brain function. Dysbiosis may be accompanied by increased intestinal permeability, translocation of bacterial components, and activation of systemic inflammatory responses[19]. Elevated circulating levels of pro-inflammatory cytokines have, in turn, been associated with alterations in neurotransmission, impaired neuroplasticity, and behavioral changes characteristic of depression and anxiety[20]. Thus, the microbiota-immune-brain axis has emerged as one of the key pathophysiological pathways in contemporary psychoneuroimmunology.

Particular attention has been devoted to the interaction between the gut microbiota and the hypothalamic-pituitary-adrenal (HPA) axis. Chronic stress

---

15 Yano J. M., Yu K., Donaldson G. P., Shastri G. G., Ann P., Ma L. et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis // *Cell*. 2015. Vol. 161, № 2. P. 264–276. DOI: 10.1016/j.cell.2015.02.047.

16 Zhao Q., Elson C. O. Adaptive immune education by gut microbiota antigens // *Immunology*. 2018. Vol. 154, № 1. P. 28–37. DOI: 10.1111/imm.12896.

17 Cui X., Cong Y. Role of gut microbiota in the development of some autoimmune diseases // *Journal of Inflammation Research*. 2025. Vol. 18. P. 4409–4419. DOI: 10.2147/JIR.S515618.

18 Feng J. J., Maddirala N. R., Saint Fleur A., Zhou F., Yu D., Wei F., Zhang Y. Gut microbiome and immune system crosstalk in chronic inflammatory diseases: a narrative review of mechanisms and therapeutic opportunities // *Microorganisms*. 2025. Vol. 13. Article 2516. DOI: 10.3390/microorganisms13112516.

19 Chen L. M., Bao C. H., Wu Y. et al. Tryptophan-kynurenine metabolism: a link between the gut and brain for depression in inflammatory bowel disease // *Journal of Neuroinflammation*. 2021. Vol. 18. Article 135. DOI: 10.1186/s12974-021-02175-2.

20 Rincel M., Aubert P., Chevalier J., Grohard P.-A., Basso L., Monchaux de Oliveira C. et al. Multi-hit early life adversity affects gut microbiota, brain and behavior in a sex-dependent manner // *Brain, Behavior, and Immunity*. 2019. Vol. 80. P. 179–192. DOI: 10.1016/j.bbi.2019.03.006.

is capable of altering intestinal permeability, gastrointestinal motility, mucus secretion, and the composition of the gut microbiota, whereas dysbiosis may potentiate or sustain the hyperactivity of the stress-response system. Consequently, a vicious cycle is established in which chronic stress and alterations of the gut microbiota mutually reinforce pathological processes.

An increasing body of evidence indicates that the establishment of the gut microbiota during early life has long-lasting consequences for the development and function of the immune, metabolic, and nervous systems[21]. Intestinal colonization begins at a very early stage of life, and its characteristics are influenced by the mode of delivery, infant feeding practices, maternal hormonal status, diet, and exposure to stress. Disturbances occurring during these critical developmental periods may alter immune programming and increase susceptibility to a wide range of diseases later in life. Experimental studies have demonstrated that early-life deprivation or chronic stress can induce persistent alterations in gut microbial composition, behavior, and brain reactivity[22]. Likewise, studies using germ-free animal models have convincingly shown that the absence of normal microbial colonization affects brain development, social behavior, stress responsiveness, and neurochemical signaling pathways[23]. These findings support the concept that the gut microbiota is not merely a passive component of the host organism but an active participant in neurodevelopment.

The association between the gut microbiota and depressive disorders has been investigated more extensively than any other aspect of the gut-brain axis. Systematic reviews and meta-analyses have consistently demonstrated that patients with depression frequently exhibit reduced microbial diversity, depletion of beneficial bacterial taxa, and impaired production of microbial metabolites involved in neuroregulation[24]. Although the findings of individual studies are not entirely consistent, the overall evidence strongly supports an association between depression and gut dysbiosis. One of the principal mechanisms implicated in the pathogenesis of depression is dysregulation of the tryptophan-kynurenine pathway. Tryptophan serves as the precursor of

---

[21] O'Mahony S. M., Hyland N. P., Dinan T. G. et al. Maternal separation as a model of brain-gut axis dysfunction // *Psychopharmacology*. 2011. Vol. 214. P. 71–88. DOI: 10.1007/s00213-010-2010-9.

[22] Karen C., Shyu D. J. H., Rajan K. E. Lactobacillus *paracasei* supplementation prevents early life stress-induced anxiety and depressive-like behavior in maternal separation model: possible involvement of microbiota-gut-brain axis in differential regulation of MicroRNA124a/132 and glutamate receptors // *Frontiers in Neuroscience*. 2021. Vol. 15. Article 719933. DOI: 10.3389/fnins.2021.719933.

[23] Nikolova V. L., Smith M. R. B., Hall L. J., Cleare A. J., Stone J. M., Young A. H. Perturbations in gut microbiota composition in psychiatric disorders: a review and meta-analysis // *JAMA Psychiatry*. 2021. Vol. 78, № 12. P. 1343–1354. DOI: 10.1001/jamapsychiatry.2021.2573.

[24] Liu L., Wang H., Chen X., Zhang Y., Zhang H., Xie P. Gut microbiota and its metabolites in depression: from pathogenesis to treatment // *EBioMedicine*. 2023. Vol. 90. Article 104527. DOI: 10.1016/j.ebiom.2023.104527.

serotonin, and a shift in its metabolism toward the kynurenine pathway may lead to reduced serotonergic neurotransmission together with the accumulation of neuroactive metabolites. The gut microbiota is capable of influencing these processes both directly through its metabolic activity and indirectly by modulating inflammatory responses[25]. Particularly compelling evidence has been obtained from experimental studies in which transplantation of the gut microbiota from patients with depression into experimental animals induced depression-like behavior accompanied by metabolic alterations[26]. These findings provide strong support for a causal, rather than merely associative, relationship between microbial dysbiosis and depressive symptomatology. Furthermore, depression is closely associated with systemic inflammation, while interactions between inflammatory biomarkers and the gut microbiome may further increase the risk of anxiety and depressive disorders.

The role of the gut microbiota has also been extensively investigated in the context of anxiety disorders. Patients with generalized anxiety disorder have been reported to exhibit an altered gut microbial profile accompanied by disturbances in metabolic and neuroimmune interactions[27]. Review articles further emphasize that alterations in the gut microbiota may be associated not only with the severity of anxiety symptoms but also with treatment response[28].

Stress is considered one of the most important factors affecting the gut–brain axis. Chronic or traumatic stress may induce persistent alterations in the gut microbiota, which subsequently contribute to the maintenance of neuroinflammation, endocrine dysregulation, and behavioral abnormalities. Recent studies have also highlighted the potential role of the gut microbiota in post-traumatic stress disorder (PTSD), where inflammation, impairment of barrier function, and alterations in microbial metabolism have been proposed as the principal underlying mechanisms.

The significance of the gut-brain axis extends far beyond affective disorders. Contemporary studies indicate that gut dysbiosis is associated with neurodegenerative diseases through mechanisms involving chronic

---

[25] Zheng P., Zeng B., Zhou C. et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism // *Molecular Psychiatry*. 2016. Vol. 21. P. 786–796. DOI: 10.1038/mp.2016.44.

[26] Jiang H., Ling Z., Zhang Y. et al. Altered gut microbiota profile in patients with generalized anxiety disorder // *Journal of Psychiatric Research*. 2018. Vol. 104. P. 130–136. DOI: 10.1016/j.jpsychires.2018.07.007.

[27] Kumar A., Pramanik J., Goyal N., Chauhan D., Sivamaruthi B. S., Prajapati B. G., Chaiyasut C. Gut microbiota in anxiety and depression: unveiling the relationships and management options // *Pharmaceuticals*. 2023. Vol. 16, № 4. Article 565. DOI: 10.3390/ph16040565.

[28] Chen C., Wang G. Q., Li D. D., Zhang F. Microbiota-gut-brain axis in neurodegenerative diseases: molecular mechanisms and therapeutic targets // *Molecular Biomedicine*. 2025. Vol. 6, № 1. Article 64. DOI: 10.1186/s43556-025-00307-1.

inflammation, oxidative stress, impaired barrier function, and alterations in microbial metabolites[29]. Likewise, changes in the gut microbiota are increasingly recognized as contributing factors in the pathogenesis of systemic inflammatory, endocrine, and cardiovascular diseases[30]. Furthermore, growing attention has been paid to the sex- and reproduction-related aspects of microbiome-host interactions. In women, the gut microbiota has been associated not only with somatic health but also with psychological well-being and reproductive health[31]. These findings underscore the need for a more individualized approach to microbiome research that takes into account age, sex, and hormonal status.

One of the most promising areas of current research is the use of psychobiotics, including probiotics, prebiotics, and other microbiome-targeted interventions capable of improving mental health through modulation of the gut-brain axis[32]. A considerable number of review articles have reported the potential efficacy of psychobiotics in the management of depression, anxiety, and other psychiatric disorders; however, the results of clinical studies remain heterogeneous and require further confirmation[33].

Another promising therapeutic strategy involves the use of postbiotics, defined as metabolites, structural components, or other bioactive products derived from microorganisms that exert beneficial biological effects without the administration of live bacteria[34]. This approach may offer a more favorable safety profile and a more predictable mechanism of action than conventional probiotic therapy, although its clinical efficacy still requires confirmation in well-designed clinical trials.

Diet is another important modifiable factor influencing the composition and function of the gut microbiota. Numerous studies have demonstrated that adherence to a Mediterranean dietary pattern is associated with a reduced

---

[29] Abdol Samat H. N., Razali N. N., Mahadzir H., Tengku Muhammad T. S., Ling K.-H., Mansor N. I., Abidin S. Z. The interplay of inflammation and gut-microbiota dysbiosis in Alzheimer's disease: mechanisms and therapeutic potential // *International Journal of Molecular Sciences*. 2025. Vol. 26. Article 8905. DOI: 10.3390/ijms26188905.

[30] Marano G., Traversi G., Gaetani E., Gasbarrini A., Mazza M. Gut microbiota in women: the secret of psychological and physical well-being // *World Journal of Gastroenterology*. 2023. Vol. 29. P. 5945–5952. DOI: 10.3748/wjg.v29.i45.5945.

[31] Sarkar A., Lehto S. M., Harty S., Dinan T. G., Cryan J. F., Burnet P. W. J. Psychobiotics and the manipulation of bacteria-gut-brain signals // *Trends in Neurosciences*. 2016. Vol. 39, № 11. P. 763–781. DOI: 10.1016/j.tins.2016.09.002.

[32] Zhou L., Foster J. A. Psychobiotics and the gut-brain axis: in the pursuit of happiness // *Neuropsychiatric Disease and Treatment*. 2015. Vol. 11. P. 715–723. DOI: 10.2147/NDT.S61997.

[33] Binda S., Tremblay A., Iqbal U. H., Kassem O., Le Barz M., Thomas V. et al. Psychobiotics and the microbiota-gut-brain axis: where do we go from here? // *Microorganisms*. 2024. Vol. 12, № 4. Article 634. DOI: 10.3390/microorganisms12040634.

[34] Liu C., Ma N., Feng Y., Zhou M., Li H., Zhang X., Ma X. From probiotics to postbiotics: concepts and applications // *Animal Research and One Health.* 2023. Vol. 1, № 1. P. 92–114. DOI: 10.1002/aro2.7.

prevalence and severity of depressive symptoms, at least in part owing to its beneficial effects on the intestinal ecosystem and inflammatory processes[35]. Consequently, dietary interventions may represent an important component of comprehensive strategies for the prevention and treatment of psychiatric disorders.

Fecal microbiota transplantation (FMT) has also emerged as an actively investigated therapeutic approach. Preclinical studies together with the first clinical trials suggest that FMT may provide therapeutic benefits in patients with depression and certain neurological disorders; however, its efficacy, long-term safety, and standardization remain subjects of ongoing investigation[36]. At present, FMT cannot be regarded as a routine therapeutic option in psychiatric practice, although it possesses considerable scientific and translational potential[37].

In summary, the gut microbiota represents a crucial regulator of the gut–brain axis and exerts profound effects on immune, neuroendocrine, and neurometabolic processes associated with mental health. The strongest body of evidence currently supports its role in depression, anxiety, and stress-related disorders, although increasing attention is being directed toward its involvement in neurodegenerative, autoimmune, and systemic diseases. Contemporary findings support the concept that gut dysbiosis may not only accompany psychiatric disorders but also actively contribute to their pathogenesis through inflammatory mechanisms, disruption of barrier integrity, alterations in tryptophan metabolism, modulation of neurotransmitter systems, and dysregulation of the stress response. At the same time, the clinical application of psychobiotics, dietary interventions, postbiotics, and fecal microbiota transplantation remains at an early stage of scientific development.

Despite substantial progress in this field, several important limitations should be acknowledged. First, the composition of the gut microbiota is profoundly influenced by diet, age, lifestyle, medication use, geographical location, and concomitant diseases, making direct comparisons among different studies challenging. Second, most clinical investigations are observational and

---

[35] Zielińska M., Łuszczki E., Michońska I., Dereń K. The Mediterranean diet and the Western diet in adolescent depression: current reports // *Nutrients*. 2022. Vol. 14, № 20. Article 4390. DOI: 10.3390/nu14204390

[36] Vasiliu O. Is fecal microbiota transplantation a useful therapeutic intervention for psychiatric disorders? A narrative review of clinical and preclinical evidence // *Current Medical Research and Opinion*. 2023. Vol. 39, № 1. P. 161–177. DOI: 10.1080/03007995.2022.2124071.

[37] Borrego-Ruiz A., Borrego J. J. Fecal microbiota transplantation as a tool for therapeutic modulation of neurological and mental disorders // *SciBase Neurology*. 2024. Vol. 2, № 2. Article 1018. DOI: 10.52768/neurology/1018.

therefore do not allow definitive conclusions regarding causal relationships. Third, the therapeutic effects of microbiome-targeted interventions demonstrate considerable interindividual variability, while standardized clinical protocols for psychobiotics, postbiotics, and fecal microbiota transplantation have yet to be established.

Overall, the gut-brain axis represents one of the most rapidly advancing areas of contemporary biomedicine, offering new opportunities for understanding the mechanisms underlying psychiatric disorders and for developing personalized strategies for their prevention and treatment.

2. Intercellular communication and methods for its investigation

Over the past decades, our understanding of the interactions between the host and microorganisms has expanded considerably. Whereas bacteria were previously regarded primarily as autonomous pathogens or commensals, increasing attention is now being paid to their ability to perceive host-derived signals and respond by altering their growth, gene expression, virulence, and colonization patterns[38]. One of the most rapidly developing fields in this area is microbial endocrinology, which investigates the effects of host hormones and neurotransmitters on microorganisms, as well as the reciprocal influence of the microbiota on host physiology[39]. Catecholamines, steroid hormones, and glucocorticoids are of particular interest because of their ability to modulate bacterial behavior, intestinal barrier function, immune activity, and the composition of the gut microbiota[40]. In turn, the gut microbiota participates in the metabolism of biologically active compounds, the production of neuroactive metabolites, and the regulation of the gut-brain axis.

Consequently, this field is of not only fundamental biological interest but also considerable clinical relevance. Therefore, the methodology for investigating these interactions cannot be confined to a single experimental approach.

Microbial endocrinology is founded on the concept that host-derived signaling molecules may serve as informational cues enabling bacteria to sense

---

[38] Sayin S. I., Wahlström A., Felin J., Jäntti S., Marschall H. U., Bamberg K. et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist // *Cell Metabolism*. 2013. Vol. 17, № 2. P. 225–235. DOI: 10.1016/j.cmet.2013.01.003

[39] Lyte M., Villageliú D., Crooker B. et al. Symposium review: microbial endocrinology – why the integration of microbes, epithelial cells, and neurochemical signals in the digestive tract matters to ruminant health // *Journal of Dairy Science*. 2018. Vol. 101. P. 5619–5628.

[40] Torres P. J., Siakowska M., Banaszewska B., Pawelczyk L., Duleba A. J., Kelley S. T., Thackray V. G. Gut microbial diversity in women with polycystic ovary syndrome correlates with hyperandrogenism // *Journal of Clinical Endocrinology & Metabolism*. 2018. Vol. 103, № 4. P. 1502–1511. DOI: 10.1210/jc.2017-02153.

the physiological state of the host. Norepinephrine, epinephrine, dopamine, sex hormones, and glucocorticoids can directly or indirectly affect microorganisms by altering their growth rate, biofilm formation, antimicrobial susceptibility, and the expression of virulence-associated genes[41]. The review by Lyte emphasized that neuroendocrine interactions between the host and the microbiota are fundamentally bidirectional: the host influences microbial communities through neurotransmitters and hormones, whereas the microbiota, in turn, modulates the functions of the nervous, immune, and endocrine systems[42]. This concept is further supported by evidence demonstrating the integration of microorganisms, intestinal epithelial cells, and neurochemical signaling within the gastrointestinal tract, which is essential for both the maintenance of physiological homeostasis and the development of disease[43].

Among hormonal factors influencing bacterial physiology, catecholamines, particularly norepinephrine and epinephrine, have been investigated most extensively. Early studies demonstrated that catecholamines stimulate the growth of Gram-negative bacteria[44]. Subsequent investigations confirmed that this phenomenon is not restricted to individual bacterial strains but is shared by a broad range of clinically important pathogens[45]. Freestone and colleagues demonstrated that catecholamine-induced growth of *Escherichia coli* O157:H7, *Salmonella enterica*, and *Yersinia enterocolitica* can be inhibited by antagonists of adrenergic and dopaminergic receptors, indicating the specificity of these signaling pathways. More recent studies have further demonstrated that norepinephrine not only accelerates bacterial growth but also enhances bacterial virulence. For example, exposure to norepinephrine increased both growth and pathogenicity in *Aeromonas hydrophila*[46]. Likewise, in *Pseudomonas aeruginosa*, norepinephrine has been shown to enhance virulence through activation of the

---

41 Luqman A. The orchestra of human bacteriome by hormones // *Microbial Pathogenesis*. 2023. Vol. 180. Article 106125. DOI: 10.1016/j.micpath.2023.106125.

42 Asano Y., Hiramoto T., Nishino R., Aiba Y., Kimura T., Yoshihara K., Koga Y., Sudo N. Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice // *American Journal of Physiology. Gastrointestinal and Liver Physiology*. 2012. Vol. 303, № 11. P. G1288–G1295. DOI: 10.1152/ajpgi.00341.2012.

43 De Vadder F., Kovatcheva-Datchary P., Goncalves D., Vinera J., Zitoun C., Duchampt A. et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits // *Cell*. 2014. Vol. 156, № 1–2. P. 84–96. DOI: 10.1016/j.cell.2013.12.016.

44 Freestone P. P., Haigh R. D., Lyte M. Blockade of catecholamine-induced growth by adrenergic and dopaminergic receptor antagonists in *Escherichia coli* O157:H7, *Salmonella enterica* and *Yersinia enterocolitica* // *BMC Microbiology*. 2007. Vol. 7. Article 8. DOI: 10.1186/1471-2180-7-8.

45 Baker J. M., Al-Nakkash L., Herbst-Kralovetz M. M. Estrogen-gut microbiome axis: physiological and clinical implications // *Maturitas*. 2017. Vol. 103. P. 45–53. DOI: 10.1016/j.maturitas.2017.06.025.

46 Zierer J., Jackson M. A., Kastenmüller G., Mangino M., Long T., Telenti A. et al. The fecal metabolome as a functional readout of the gut microbiome // *Nature Genetics*. 2018. Vol. 50, № 6. P. 790–795. DOI: 10.1038/s41588-018-0135-7.

quorum sensing regulatory network, particularly the las signaling pathway[47]. Particularly compelling findings have been reported for enterotoxigenic *E. coli*, in which norepinephrine and epinephrine simultaneously influenced bacterial growth, antimicrobial susceptibility, biofilm formation, and virulence gene expression[48]. These observations indicate that bacterial responses to host hormones extend far beyond isolated physiological effects and instead involve comprehensive remodeling of the bacterial phenotype.

The virulence of numerous bacterial species is regulated through quorum sensing, an intercellular communication mechanism that enables bacterial populations to coordinate gene expression according to cell density[49]. This regulatory system controls the production of toxins, extracellular enzymes, adhesins, biofilm formation, and invasive capacity. Importantly, host-derived signals are capable of interfering with these bacterial communication networks. Norepinephrine activates signaling pathways associated with quorum sensing, as demonstrated in *P. aeruginosa*. Conversely, certain sex hormones may function as inhibitors of quorum sensing. Beury-Cirou and co-authors demonstrated that supraphysiological concentrations of human sex hormones suppress quorum sensing signaling[50]. These findings open promising prospects for the development of anti-virulence therapeutic strategies aimed not at eliminating bacteria but at disrupting their coordinated pathogenic behavior.

Sex steroids represent another important group of molecules involved in modulating host-microbe interactions. The review by García-Gómez and co-authors emphasizes that estrogens, progesterone, and androgens can influence bacterial adhesion, growth, and pathogenicity, while simultaneously modulating host immune responses. At the same time, sex hormones also affect the composition of the gut microbiota itself. Experimental studies in mice have demonstrated pronounced sex-related differences in gut microbial composition

---

[47] Söderholm J. D., Perdue M. H. Stress and gastrointestinal tract. II. Stress and intestinal barrier function // *American Journal of Physiology. Gastrointestinal and Liver Physiology*. 2001. Vol. 280, № 1. P. G7–G13. DOI: 10.1152/ajpgi.2001.280.1.G7.

[48] Niu L., Gao M., Wen S., Wang F., Shangguan H., Guo Z. et al. Effects of catecholamine stress hormones norepinephrine and epinephrine on growth, antimicrobial susceptibility, biofilm formation, and gene expressions of enterotoxigenic *Escherichia coli* // *International Journal of Molecular Sciences*. 2023. Vol. 24, № 21. Article 15646. DOI: 10.3390/ijms242115646.

[49] Hegde M., Wood T. K., Jayaraman A. The neuroendocrine hormone norepinephrine increases *Pseudomonas aeruginosa* PA14 virulence through the *las* quorum-sensing pathway // *Applied Microbiology and Biotechnology*. 2009. Vol. 84, № 4. P. 763–776. DOI: 10.1007/s00253-009-2045-1.

[50] García-Gómez E., González-Pedrajo B., Camacho-Arroyo I. Role of sex steroid hormones in bacterial-host interactions // *BioMed Research International*. 2013. Vol. 2013. Article 928290. DOI: 10.1155/2013/928290.

together with hormone-dependent alterations in microbial community structure[51]. In women with polycystic ovary syndrome, gut microbial diversity has been shown to be associated with hyperandrogenism. These findings indicate that hormonal status represents one of the major determinants shaping the microbial landscape of the host.

Particular attention has recently been directed toward the estrogen-microbiome axis. Several review articles have highlighted the pivotal role of the gut microbiota in estrogen metabolism, demonstrating that alterations in microbial composition may influence estrogen homeostasis and consequently affect the risk of hormone-dependent diseases[52]. This issue has become especially relevant in oncology, particularly in relation to breast cancer[53].

Contemporary concepts of the gut microbiota extend well beyond the taxonomic characterization of bacterial communities. Metagenomic and metatranscriptomic investigations have revealed the remarkable functional potential of the intestinal microbiota in metabolism, the synthesis of signaling molecules, and immune regulation. Gut microorganisms are capable of producing or biotransforming a wide variety of neuroactive compounds. For example, several bacterial taxa have been shown to regulate the production of γ-aminobutyric acid (GABA), one of the principal inhibitory neurotransmitters in the central nervous system. Furthermore, experimental studies in mice have demonstrated that the gut microbiota contributes to the pool of free catecholamines within the intestinal lumen. This observation is particularly significant because local catecholamine concentrations may directly influence the physiology of both commensal and pathogenic microorganisms. In addition, the gut microbiota participates in bile acid metabolism and in the production of short-chain fatty acids (SCFAs), which regulate numerous metabolic pathways and contribute to gut-brain communication. Collectively, these findings indicate that the gut microbiota should be regarded not as a passive recipient of endocrine signals but as an active component of an integrated neuroendocrine signaling network.

---

[51] Org E., Mehrabian M., Parks B. W., Shipkova P., Liu X., Drake T. A., Lusis A. J. Sex differences and hormonal effects on gut microbiota composition in mice // *Gut Microbes*. 2016. Vol. 7, № 4. P. 313–322. DOI: 10.1080/19490976.2016.1203502.

[52] Saravinovska K., Santi D., Costantino F., Prete A., Šojat A. S., Spaggiari G. et al. The impact of estrogen status on the gut microbiome: a systematic review and meta-analysis // *Frontiers in Endocrinology*. 2026. Vol. 17. Article 1780806. DOI: 10.3389/fendo.2026.1780806.

[53] Kwa M., Hussey G., Novik Y. et al. Evaluation of the gut microbiome and sex hormones in postmenopausal women with newly diagnosed hormone receptor-positive breast cancer versus healthy women: a prospective case-control study // *Journal of Cancer Research and Clinical Oncology*. 2025. Vol. 151. Article 275. DOI: 10.1007/s00432-025-06338-z.

Stress-induced physiological responses profoundly affect gastrointestinal function. It is well established that stress compromises intestinal barrier integrity, increases epithelial permeability, and promotes inflammatory processes within the gastrointestinal tract. Likewise, experimental models have demonstrated that chronic social stress induces significant alterations in gut microbial composition[54].

Glucocorticoids and sex hormones also play essential roles in maintaining epithelial barrier function. Glucocorticoids regulate the expression of tight junction proteins and contribute to the preservation of epithelial integrity[55], whereas estradiol decreases colonic permeability through activation of estrogen receptor β (ERβ) and enhanced expression of intercellular junction proteins[56]. Moreover, glucocorticoids exert potent anti-inflammatory effects, including the induction of endogenous negative regulators of inflammatory signaling pathways[57]. Consequently, preservation of intestinal barrier integrity is crucial for maintaining controlled interactions between the gut microbiota and the host immune system. Disruption of this barrier facilitates bacterial translocation, promotes chronic inflammation, and alters host-microbe interactions. Within this context, hormonal signaling acquires a dual biological role by simultaneously affecting bacterial physiology and host tissues.

Stress-induced physiological responses profoundly affect gastrointestinal function. It has been well established that stress disrupts intestinal barrier integrity, increases epithelial permeability, and promotes inflammatory processes within the gastrointestinal tract. Likewise, social stress has been shown to alter the composition of the gut microbiota in experimental animal models.

Glucocorticoids and sex hormones are also capable of modulating epithelial barrier function. Glucocorticoids regulate the expression of tight junction proteins and contribute to the maintenance of epithelial integrity, whereas estradiol reduces colonic permeability through activation of estrogen receptor β and increased

---

[54] Bailey M. T., Dowd S. E., Galley J. D., Hufnagle A. R., Allen R. G., Lyte M. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation // *Brain, Behavior, and Immunity*. 2011. Vol. 25, № 3. P. 397–407. DOI: 10.1016/j.bbi.2010.10.023.

[55] Fischer A., Gluth M., Weege F., Pape U. F., Wiedenmann B., Baumgart D. C., Theuring F. Glucocorticoids regulate barrier function and claudin expression in intestinal epithelial cells via MKP-1 // *American Journal of Physiology. Gastrointestinal and Liver Physiology*. 2014. Vol. 306, № 3. P. G218–G228. DOI: 10.1152/ajpgi.00095.2013.

[56] Braniste V., Leveque M., Buisson-Brenac C., Bueno L., Fioramonti J., Houdeau E. Oestradiol decreases colonic permeability through oestrogen receptor β-mediated up-regulation of occludin and junctional adhesion molecule-A in epithelial cells // *Journal of Physiology*. 2009. Vol. 587, Pt 13. P. 3317–3328. DOI: 10.1113/jphysiol.2009.169300.

[57] Miyata M., Lee J. Y., Susuki-Miyata S., Wang W. Y., Xu H., Kai H. et al. Glucocorticoids suppress inflammation via the upregulation of negative regulator IRAK-M // *Nature Communications*. 2015. Vol. 6. Article 6062. DOI: 10.1038/ncomms7062.

expression of intercellular junction proteins. Moreover, glucocorticoids exert potent anti-inflammatory effects, including the induction of negative regulators of inflammatory signaling pathways. Consequently, preservation of intestinal barrier integrity is essential for maintaining controlled interactions between the gut microbiota and the host immune system. Disruption of this barrier may facilitate bacterial translocation, promote chronic inflammation, and alter host–microbe interactions. Within this context, hormonal signaling assumes a dual role by simultaneously affecting both bacterial physiology and host tissues.

Germ-free animal models and advanced cell culture systems have become indispensable tools for investigating hormone–microbe interactions. Studies employing germ-free mice have demonstrated the fundamental contribution of the gut microbiota to host physiology, including the development and function of the nervous, immune, and metabolic systems. Such experimental models make it possible to distinguish microbiota-dependent effects from other environmental influences. Furthermore, co-culture models incorporating intestinal enteroids and macrophages have been developed to more accurately reproduce the physiological conditions of the intestinal mucosa and its interactions with pathogenic microorganisms. These advanced experimental systems provide valuable opportunities for investigating how hormones simultaneously influence bacterial virulence, epithelial barrier permeability, and host immune responses.

Based on the available evidence, microbial endocrinology has established a fundamentally new perspective on the interactions between the host and microorganisms. Hormones not only regulate human physiology but can also directly influence bacterial growth, virulence, biofilm formation, and signaling pathways. Consequently, hormonal signals may substantially modify the course of infectious processes. Catecholamines are of particular importance because they enhance the pathogenic potential of numerous bacterial species, whereas sex hormones and glucocorticoids influence both the composition and functional activity of the gut microbiota as well as the integrity of the intestinal barrier. Catecholamines promote bacterial growth and virulence, while sex hormones and glucocorticoids can modify microbial characteristics and simultaneously regulate epithelial barrier function and host immune responses. Clinically, these observations imply that psychoemotional stress, endocrine disorders, pregnancy, menopause, and hormone therapy may all influence the composition of the gut microbiota and susceptibility to infectious diseases.

From a translational perspective, these findings open several promising avenues for future clinical application:

• prediction of infectious disease risk based on an individual's hormonal profile;

• development of anti-virulence therapeutic strategies targeting quorum sensing rather than bacterial viability;

• modulation of the gut microbiota through dietary interventions, probiotics, and other microbiome-based approaches;

• implementation of personalized medicine strategies integrating microbiome profiling with endocrine assessment.

Conversely, the gut microbiota should be regarded as an active participant in neuroendocrine communication, capable of synthesizing, transforming, and metabolizing biologically active molecules while influencing host metabolism, immune responses, and the function of the gut-brain axis. Collectively, these findings indicate that the interactions among hormones, the gut microbiota, and infectious processes constitute a highly complex, multilevel biological network whose comprehensive understanding is of considerable importance for contemporary biomedicine.

Despite substantial advances in this field, numerous mechanisms remain insufficiently understood. In particular, further studies are required to define the concentration-dependent effects of hormones, determine the species specificity of bacterial responses, and clarify the discrepancies between findings obtained *in vitro*, in animal models, and under clinical conditions. Therefore, the development of an integrated methodological framework for investigating both the direct and indirect effects of hormones on microorganisms-including a clear understanding of the strengths and limitations of individual experimental approaches and the rational combination of complementary methodologies-will improve the quality of experimental evidence and enhance the reliability of scientific conclusions.

3. Effects of different cortisol concentrations on selected properties of nosocomial pathogens

The effects of cortisol on bacterial physiology were modeled by supplementing the culture medium with appropriate amounts of hydrocortisone acetate (2.5%, 25 mg/mL). Physiologically relevant cortisol concentrations were selected based on published data describing physiological cortisol levels in human saliva[58]. Salivary cortisol concentrations under resting conditions are approximately 1–10 ng/mL (≈3–30 nmol/L), increase to 10–30 ng/mL (≈30–110 nmol/L) during acute stress, remain within 10–20 ng/mL (≈30–55 nmol/L) during prolonged moderate stress, and reach 20–30 ng/mL (≈55–80 nmol/L) during prolonged severe stress58. Accordingly, final cortisol

[58] Duran-Pinedo A. E., Solbiati J., Frias-Lopez J. The stress hormone cortisol induces virulence in the oral microbiome // *NPJ Biofilms and Microbiomes*. 2018. Vol. 4. Article 25. DOI: 10.1038/s41522-018-0068-z.

concentrations of 5, 15, and 25 ng/mL were selected for the present study. Stock solutions were prepared by serial dilution in sterile phosphate-buffered saline (PBS) and subsequently added to the culture medium to obtain the desired final concentrations.

Reference and clinical strains of *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* served as the study organisms. Bacterial suspensions were prepared from 24-hour cultures and adjusted to an optical density corresponding to 1,0 McFarland units. The effects of cortisol on bacterial growth were evaluated by determining both the increase in bacterial biomass and the number of microbial cells after 16-h of incubation using conventional microbiological methods (S. J. Pirt, 1978). Glucose utilization was determined by the glucose oxidase method based on the amount of glucose oxidized in the culture medium using commercial reagent kits manufactured by Filisit-Diagnostics Ltd. (Ukraine) according to the manufacturer's instructions with our previously described modification[59].

The intensity of metabolic activity represents one of the principal indicators of microbial growth potential and is therefore of particular importance when investigating the effects of stress hormones on microorganisms. It may also serve as an indicator of the potential growth rate of different subpopulations of infectious agents. Like all living organisms, prokaryotes require a continuous supply of energy to sustain essential metabolic processes. Since glucose is the universal energy source for most organisms, the first stage of the present study was to determine the amount of glucose utilized by the investigated microorganisms (Figure 1).

The results presented in Table 1 demonstrated that supplementation of the culture medium with cortisol increased glucose utilization in all investigated bacterial strains compared with the untreated controls. In most isolates, a clear dose-dependent pattern was observed, with progressively greater glucose consumption as the cortisol concentration increased from 5 ng/mL to 25 ng/mL.

Among the *S. aureus* strains, the lowest glucose utilization was observed in the reference strain *S. aureus* ATCC 25923. Compared with the control, glucose consumption increased 1.7-fold ($p < 0,05$), 1.9-fold ($p < 0.01$), and 2.1-fold ($p < 0.01$) following supplementation with 5, 15, and 25 ng/mL cortisol, respectively. A similar dose-dependent response was observed in the clinical isolates *S. aureus* 68 and *S. aureus* 172. In *S. aureus* 68, glucose utilization increased 1.6-fold ($p < 0.05$), 1.8-fold ($p < 0.05$), and 2.4-fold ($p < 0.01$),

[59] Каліниченко С. В., Рижкова Т. А., Антушева Т. І., Скляр Н. І., Коротких О. О. Метод визначення катаболічної активності мікроорганізмів за кількістю окисленої глюкози // *Вісник проблем біології і медицини*. 2012. Вип. 4, т. 2 (97). С. 150–153.

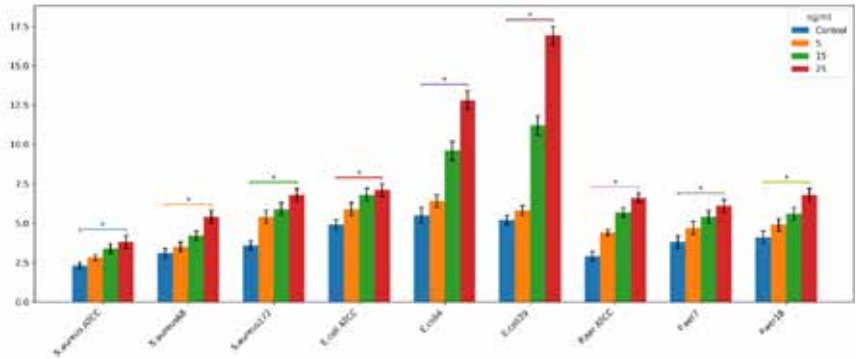


Fig. 1. Glucose utilization by the investigated bacterial strains

whereas in *S. aureus* 172 the corresponding increases were 1.8-fold ($p < 0.05$), 2.0-fold ($p < 0.01$), and 2.1-fold ($p < 0.01$).

The most pronounced stimulation of metabolic activity was observed in the *E. coli* strains. In the reference strain *E. coli* ATCC 25922, glucose utilization increased 1.8-fold ($p < 0.05$), 2.4-fold ($p < 0.01$), and 3.4-fold ($p < 0.01$) compared with the control following the addition of 5, 15, and 25 ng/mL cortisol, respectively. However, the clinical isolates *E. coli* 4 and *E. coli* 29 exhibited the strongest response to cortisol exposure. Specifically, glucose utilization by *E. coli* 4 increased 2.7-fold ($p < 0.01$), 7.6-fold ($p < 0.001$), and 26.3-fold ($p < 0.001$), whereas *E. coli* 29 demonstrated increases of 2.4-fold ($p < 0.01$), 4.7-fold ($p < 0.01$), and 10.7-fold ($p < 0.001$) following supplementation with 5, 15, and 25 ng/mL cortisol, respectively. These findings demonstrate a pronounced dose-dependent stimulatory effect of cortisol on the metabolic activity of *E. coli*.

A similar pattern was observed among the *P. aeruginosa* strains. In the reference strain *P. aeruginosa* ATCC 27853, glucose utilization increased 1.9-fold ($p < 0.05$), 2.1-fold ($p < 0.01$), and 2.4-fold ($p < 0.01$) following supplementation with 5, 15, and 25 ng/mL cortisol, respectively. In the clinical isolates *P. aeruginosa* 7 and *P. aeruginosa* 18, glucose consumption also increased progressively, reaching 2.2–2.9-fold above the control values depending on cortisol concentration ($p < 0.05$). These observations confirm that cortisol enhances metabolic activity in representatives of this species as well.

Overall, the obtained results demonstrate that physiologically relevant concentrations of cortisol stimulate glucose utilization by the investigated bacterial strains, indicating enhanced metabolic activity under exposure to this stress hormone. The most pronounced response was observed in the clinical

E. coli isolates, suggesting species-specific differences in bacterial adaptation to stress hormones and a potentially greater capacity of clinical isolates to respond to elevated cortisol concentrations.

Effects of cortisol on bacterial biomass accumulation. In addition to glucose utilization, bacterial biomass accumulation was evaluated as an integral indicator of microbial growth under exposure to different cortisol concentrations. The results are presented in Figure 2.

The findings demonstrated that cortisol stimulated biomass accumulation in all investigated bacterial strains. Similar to glucose utilization, the magnitude of the response depended on both cortisol concentration and bacterial species.

Among the *S. aureus* strains, supplementation of the culture medium with cortisol resulted in a gradual increase in biomass accumulation. The reference strain *S. aureus* ATCC 25923 exhibited a moderate increase compared with the untreated control, whereas the clinical isolates *S. aureus* 68 and *S. aureus* 172 showed a more pronounced response, particularly at cortisol concentrations of 15 ng/mL and 25 ng/mL. These observations indicate that clinical isolates may possess greater sensitivity to stress hormone-mediated regulation of bacterial growth.

The strongest stimulatory effect was again observed in the *E. coli* strains. Biomass accumulation increased significantly following exposure to all tested cortisol concentrations, with the greatest effect recorded in the clinical isolates. These findings were consistent with the glucose utilization data, indicating that enhanced carbohydrate metabolism was accompanied by increased bacterial proliferation. The concordance between these two parameters suggests that cortisol promotes not only metabolic activation but also bacterial growth.

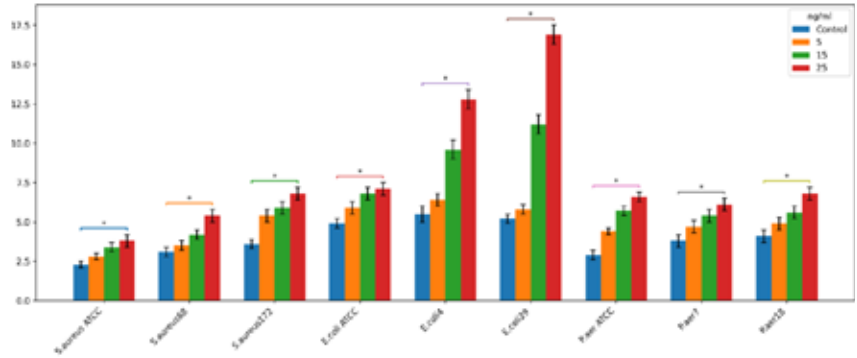


Fig. 2. Effects of cortisol on biomass accumulation in the investigated bacterial strains

A comparable pattern was observed in *P. aeruginosa*. Both the reference strain and the clinical isolates demonstrated increased biomass accumulation following cortisol supplementation, although the magnitude of the response was less pronounced than that observed in *E. coli*. Nevertheless, the overall trend remained dose-dependent, with the highest biomass values recorded after exposure to 25 ng/mL cortisol.

Collectively, these results demonstrate that physiologically relevant cortisol concentrations stimulate bacterial proliferation in representatives of all three investigated species. Moreover, clinical isolates consistently exhibited a stronger response than the corresponding reference strains, suggesting that bacteria circulating in hospital environments may possess an enhanced capacity to perceive and respond to host-derived endocrine signals.

The parallel increase in glucose utilization and biomass accumulation further supports the hypothesis that cortisol induces coordinated activation of bacterial metabolism rather than isolated stimulation of individual metabolic pathways. These observations are consistent with the contemporary concept of microbial endocrinology, according to which stress hormones function as signaling molecules capable of modifying bacterial physiology, adaptation, and pathogenic potential.

The present study demonstrated that physiologically relevant cortisol concentrations significantly influenced the metabolic activity and growth characteristics of the investigated nosocomial pathogens. Exposure to cortisol resulted in enhanced glucose utilization together with increased biomass accumulation in *S. aureus*, *E. coli*, and *P. aeruginosa*. The most pronounced response was observed in the clinical *E. coli* isolates, indicating marked species-specific differences in bacterial sensitivity to glucocorticoid signaling.

The obtained findings are consistent with the current understanding of microbial endocrinology, which recognizes host hormones as biologically active signaling molecules capable of regulating bacterial physiology. Previous investigations have primarily focused on the effects of catecholamines, particularly norepinephrine and epinephrine, on bacterial growth and virulence. The present results extend these observations by demonstrating that glucocorticoids, specifically cortisol, also exert measurable stimulatory effects on bacterial metabolism.

One of the principal observations of this study was the close association between enhanced glucose utilization and increased biomass accumulation. These findings suggest that cortisol stimulates coordinated metabolic activation rather than isolated enhancement of glucose consumption. Increased glucose utilization provides microorganisms with additional energy resources required for biosynthesis, cell division, and adaptive responses to environmental changes.

Consequently, cortisol appears to facilitate the overall physiological activity of bacterial cells.

Another important finding was the greater responsiveness of clinical isolates compared with the corresponding reference strains. Hospital-associated microorganisms are continuously exposed to complex environmental stressors, including antimicrobial therapy, disinfectants, immune defense mechanisms, and hormonal fluctuations in hospitalized patients. Such conditions may promote the selection of bacterial populations with enhanced adaptive capacity, including increased sensitivity to host-derived endocrine signals. This hypothesis warrants further investigation at both molecular and genomic levels.

The observed species-specific differences also deserve attention. Clinical *E. coli* isolates exhibited the strongest response to cortisol, whereas *S. aureus* and *P. aeruginosa* demonstrated more moderate but still statistically significant effects. These differences may reflect variations in regulatory systems responsible for hormone recognition, metabolic adaptation, and signal transduction. Future studies employing transcriptomic, proteomic, and metabolomic approaches will be required to identify the molecular mechanisms underlying these responses.

Overall, the present findings support the concept that host stress hormones should be regarded not merely as physiological regulators of the human organism but also as important environmental signals capable of influencing bacterial behavior. These observations further strengthen the theoretical framework of microbial endocrinology and provide additional evidence for the existence of complex bidirectional communication between the host and microorganisms.

The findings of this study have important implications for both experimental microbiology and clinical medicine. Demonstration of the stimulatory effects of physiologically relevant cortisol concentrations on bacterial metabolism suggests that psychoemotional stress and endocrine disturbances may influence not only host immune responses but also the biological properties of opportunistic and pathogenic microorganisms.

Understanding the mechanisms by which stress hormones modulate bacterial physiology may contribute to the development of innovative approaches for the prevention and treatment of infectious diseases. In particular, modulation of endocrine–microbial interactions may represent a promising strategy for reducing bacterial virulence without exerting direct selective pressure on microbial viability, thereby potentially limiting the emergence of antimicrobial resistance.

Furthermore, these findings support the integration of microbiological, endocrinological, and immunological approaches within the framework of personalized medicine. Assessment of hormonal status together with microbiome characteristics may improve the prediction of infection risk, optimize therapeutic decision-making, and facilitate the development of individualized preventive interventions.

CONCLUSIONS

The findings of the present study provide additional evidence supporting the contemporary concept of microbial endocrinology, according to which host hormones function not only as regulators of physiological processes but also as signaling molecules capable of directly influencing bacterial physiology.

Physiologically relevant concentrations of cortisol significantly stimulated glucose utilization and biomass accumulation in all investigated bacterial strains, indicating activation of their metabolic activity. The magnitude of this response depended on both the bacterial species and the origin of the isolate. The most pronounced effects were observed in the clinical isolates of *E. coli*, suggesting that hospital-associated strains may possess an enhanced capacity to recognize and respond to host-derived endocrine signals.

The observed parallel increase in glucose utilization and bacterial biomass suggests that cortisol promotes coordinated metabolic activation rather than isolated stimulation of individual biochemical pathways. These findings indicate that glucocorticoids may contribute to bacterial adaptation under stress-associated conditions and potentially influence the persistence and progression of infectious processes.

The present results expand current knowledge regarding the biological effects of glucocorticoids on clinically significant microorganisms and further support the concept of bidirectional communication between the host and its microbiota. Collectively, these findings emphasize that interactions among hormones, microorganisms, and the host represent an integrated regulatory network rather than independent biological processes.

Future investigations should focus on elucidating the molecular mechanisms underlying cortisol-mediated bacterial responses, including transcriptomic, proteomic, and metabolomic analyses, as well as the identification of bacterial receptors and signaling pathways involved in hormone perception. Such studies will contribute to a more comprehensive understanding of host–microbe communication and may facilitate the development of novel preventive and therapeutic strategies aimed at modulating microbial virulence through interference with endocrine signaling.

SUMMARY

The present study highlights the importance of considering hormones as integral components of host-microbe communication. Contemporary evidence indicates that microorganisms are capable of perceiving endocrine signals and adapting their metabolic and physiological activities accordingly. Therefore, microbial endocrinology represents a rapidly evolving interdisciplinary field that integrates microbiology, endocrinology, immunology, and systems biology.

A deeper understanding of the molecular basis of host-microbiota interactions will not only improve our knowledge of microbial pathogenesis but may also provide the foundation for a new generation of microbiome-based diagnostic, preventive, and therapeutic strategies.

Bibliography

1. Brunet J.-F. Gaskell, Langley, and the "para-sympathetic" idea // *eLife*. 2025. Vol. 14. DOI: 10.7554/eLife.104826.

2. Zhang J., Fallon M. B. Hepatopulmonary syndrome: update on pathogenesis and clinical features // *Nature Reviews Gastroenterology & Hepatology*. 2012. Vol. 9, № 9. P. 539–549. DOI: 10.1038/nrgastro.2012.123.

3. Appleton J. The Gut-Brain Axis: Influence of Microbiota on Mood and Mental Health // *Integrative Medicine (Encinitas)*. 2018. Vol. 17, № 4. P. 28–32.

4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis // *Journal of Hepatology*. 2017. Vol. 67, № 1. P. 145–172. DOI: 10.1016/j.jhep.2017.03.022.

5. Clapp M., Aurora N., Herrera L., Bhatia M., Wilen E., Wakefield S. Gut microbiota's effect on mental health: The gut-brain axis // *Clinical Practice*. 2017. Vol. 7, № 4. Article 987. DOI: 10.4081/cp.2017.987.

6. Madison A., Kiecolt-Glaser J. K. Stress, depression, diet, and the gut microbiota: human-bacteria interactions at the core of psychoneuroimmunology and nutrition // *Current Opinion in Behavioral Sciences*. 2019. Vol. 28. P. 105–110. DOI: 10.1016/j.cobeha.2019.01.011.

7. Ronan V., Yeasin R., Claud E. C. Childhood development and the microbiome: the intestinal microbiota in maintenance of health and development of disease during childhood development // *Gastroenterology*. 2021. Vol. 160, № 2. P. 495–506. DOI: 10.1053/j.gastro.2020.08.065.

8. Irum N., Afzal T., Faraz M. H., Aslam Z., Rasheed F. The role of gut microbiota in depression: an analysis of the gut-brain axis // *Frontiers in Behavioral Neuroscience*. 2023. Vol. 17. Article 1185522. DOI: 10.3389/fnbeh.2023.1185522.

9. Wang Q., Yang Q., Liu X. The microbiota-gut-brain axis and neurodevelopmental disorders // *Protein & Cell*. 2023. Vol. 14, № 10. P. 762–775. DOI: 10.1093/procel/pwad026.

10. Liu Z., Lei M., Bai Y. Chronic stress mediates inflammatory cytokines alterations and its role in tumorigenesis // *Journal of Inflammation Research*. 2025. Vol. 18. P. 1067–1090. DOI: 10.2147/JIR.S485159.

11. Rusch J. A., Layden B. T., Dugas L. R. Signalling cognition: the gut microbiota and hypothalamic-pituitary-adrenal axis // *Frontiers in Endocrinology*. 2023. Vol. 14. Article 1130689. DOI: 10.3389/fendo.2023.1130689.

12. Rutsch A., Kantsjö J. B., Ronchi F. The Gut-Brain Axis: How Microbiota and Host Inflammasome Influence Brain Physiology and Pathology // *Frontiers in Immunology*. 2020. Vol. 11. Article 604179. DOI: 10.3389/fimmu.2020.604179.

13. Dockray G. J. Enteroendocrine cell signalling via the vagus nerve // *Current Opinion in Pharmacology*. 2013. Vol. 13, № 6. P. 954–958. DOI: 10.1016/j.coph.2013.09.007.

14. Tian P., Yang W., Guo X., Wang T., Tan S., Sun R. et al. Early life gut microbiota sustains liver-resident natural killer cells maturation via the butyrate–IL-18 axis // *Nature Communications*. 2023. Vol. 14. Article 1710. DOI: 10.1038/s41467-023-37419-7.

15. Yano J. M., Yu K., Donaldson G. P., Shastri G. G., Ann P., Ma L. et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis // *Cell*. 2015. Vol. 161, № 2. P. 264–276. DOI: 10.1016/j.cell.2015.02.047.

16. Zhao Q., Elson C. O. Adaptive immune education by gut microbiota antigens // *Immunology*. 2018. Vol. 154, № 1. P. 28–37. DOI: 10.1111/imm.12896.

17. Cui X., Cong Y. Role of gut microbiota in the development of some autoimmune diseases // *Journal of Inflammation Research*. 2025. Vol. 18. P. 4409–4419. DOI: 10.2147/JIR.S515618.

18. Feng J. J., Maddirala N. R., Saint Fleur A., Zhou F., Yu D., Wei F., Zhang Y. Gut microbiome and immune system crosstalk in chronic inflammatory diseases: a narrative review of mechanisms and therapeutic opportunities // *Microorganisms*. 2025. Vol. 13. Article 2516. DOI: 10.3390/microorganisms13112516.

19. Chen L. M., Bao C. H., Wu Y. et al. Tryptophan-kynurenine metabolism: a link between the gut and brain for depression in inflammatory bowel disease // *Journal of Neuroinflammation*. 2021. Vol. 18. Article 135. DOI: 10.1186/s12974-021-02175-2.

20. Rincel M., Aubert P., Chevalier J., Grohard P.-A., Basso L., Monchaux de Oliveira C. et al. Multi-hit early life adversity affects gut microbiota, brain and behavior in a sex-dependent manner // *Brain, Behavior, and Immunity*. 2019. Vol. 80. P. 179–192. DOI: 10.1016/j.bbi.2019.03.006.

21. O'Mahony S. M., Hyland N. P., Dinan T. G. et al. Maternal separation as a model of brain-gut axis dysfunction // *Psychopharmacology*. 2011. Vol. 214. P. 71–88. DOI: 10.1007/s00213-010-2010-9.

22. Karen C., Shyu D. J. H., Rajan K. E. Lactobacillus *paracasei* supplementation prevents early life stress-induced anxiety and depressive-like behavior in maternal separation model: possible involvement of microbiota-gut-brain axis in differential regulation of MicroRNA124a/132 and glutamate receptors // *Frontiers in Neuroscience*. 2021. Vol. 15. Article 719933. DOI: 10.3389/fnins.2021.719933.

23. Nikolova V. L., Smith M. R. B., Hall L. J., Cleare A. J., Stone J. M., Young A. H. Perturbations in gut microbiota composition in psychiatric disorders: a review and meta-analysis // *JAMA Psychiatry*. 2021. Vol. 78, № 12. P. 1343–1354. DOI: 10.1001/jamapsychiatry.2021.2573.

24. Liu L., Wang H., Chen X., Zhang Y., Zhang H., Xie P. Gut microbiota and its metabolites in depression: from pathogenesis to treatment // *EBioMedicine*. 2023. Vol. 90. Article 104527. DOI: 10.1016/j.ebiom.2023.104527.

25. Zheng P., Zeng B., Zhou C. et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism // *Molecular Psychiatry*. 2016. Vol. 21. P. 786–796. DOI: 10.1038/mp.2016.44.

26. Jiang H., Ling Z., Zhang Y. et al. Altered gut microbiota profile in patients with generalized anxiety disorder // *Journal of Psychiatric Research*. 2018. Vol. 104. P. 130–136. DOI: 10.1016/j.jpsychires.2018.07.007.

27. Kumar A., Pramanik J., Goyal N., Chauhan D., Sivamaruthi B. S., Prajapati B. G., Chaiyasut C. Gut microbiota in anxiety and depression: unveiling the relationships and management options // *Pharmaceuticals*. 2023. Vol. 16, № 4. Article 565. DOI: 10.3390/ph16040565.

28. Chen C., Wang G. Q., Li D. D., Zhang F. Microbiota-gut-brain axis in neurodegenerative diseases: molecular mechanisms and therapeutic targets // *Molecular Biomedicine*. 2025. Vol. 6, № 1. Article 64. DOI: 10.1186/s43556-025-00307-1.

29. Abdol Samat H. N., Razali N. N., Mahadzir H., Tengku Muhammad T. S., Ling K.-H., Mansor N. I., Abidin S. Z. The interplay of inflammation and gut-microbiota dysbiosis in Alzheimer's disease: mechanisms and therapeutic potential // *International Journal of Molecular Sciences*. 2025. Vol. 26. Article 8905. DOI: 10.3390/ijms26188905.

30. Marano G., Traversi G., Gaetani E., Gasbarrini A., Mazza M. Gut microbiota in women: the secret of psychological and physical well-being // *World Journal of Gastroenterology*. 2023. Vol. 29. P. 5945–5952. DOI: 10.3748/wjg.v29.i45.5945.

31. Sarkar A., Lehto S. M., Harty S., Dinan T. G., Cryan J. F., Burnet P. W. J. Psychobiotics and the manipulation of bacteria-gut-brain signals // *Trends in Neurosciences*. 2016. Vol. 39, № 11. P. 763–781. DOI: 10.1016/j.tins.2016.09.002.

32. Zhou L., Foster J. A. Psychobiotics and the gut-brain axis: in the pursuit of happiness // *Neuropsychiatric Disease and Treatment*. 2015. Vol. 11. P. 715–723. DOI: 10.2147/NDT.S61997.

33. Binda S., Tremblay A., Iqbal U. H., Kassem O., Le Barz M., Thomas V. et al. Psychobiotics and the microbiota-gut-brain axis: where do we go from here? // *Microorganisms*. 2024. Vol. 12, № 4. Article 634. DOI: 10.3390/microorganisms12040634.

34. Liu C., Ma N., Feng Y., Zhou M., Li H., Zhang X., Ma X. From probiotics to postbiotics: concepts and applications // *Animal Research and One Health*. 2023. Vol. 1, № 1. P. 92–114. DOI: 10.1002/aro2.7.

35. Zielińska M., Łuszczki E., Michońska I., Dereń K. The Mediterranean diet and the Western diet in adolescent depression: current reports // *Nutrients*. 2022. Vol. 14, № 20. Article 4390. DOI: 10.3390/nu14204390.

36. Vasiliu O. Is fecal microbiota transplantation a useful therapeutic intervention for psychiatric disorders? A narrative review of clinical and preclinical evidence // *Current Medical Research and Opinion*. 2023. Vol. 39, № 1. P. 161–177. DOI: 10.1080/03007995.2022.2124071.

37. Borrego-Ruiz A., Borrego J. J. Fecal microbiota transplantation as a tool for therapeutic modulation of neurological and mental disorders // *SciBase Neurology*. 2024. Vol. 2, № 2. Article 1018. DOI: 10.52768/neurology/1018.

38. Sayin S. I., Wahlström A., Felin J., Jäntti S., Marschall H. U., Bamberg K. et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist // *Cell Metabolism*. 2013. Vol. 17, № 2. P. 225–235. DOI: 10.1016/j.cmet.2013.01.003.

39. Lyte M., Villageliú D., Crooker B. et al. Symposium review: microbial endocrinology — why the integration of microbes, epithelial cells, and neurochemical signals in the digestive tract matters to ruminant health // *Journal of Dairy Science*. 2018. Vol. 101. P. 5619–5628.

40. Torres P. J., Siakowska M., Banaszewska B., Pawelczyk L., Duleba A. J., Kelley S. T., Thackray V. G. Gut microbial diversity in women with polycystic ovary syndrome correlates with hyperandrogenism // *Journal of Clinical Endocrinology & Metabolism*. 2018. Vol. 103, № 4. P. 1502–1511. DOI: 10.1210/jc.2017-02153.

41. Luqman A. The orchestra of human bacteriome by hormones // *Microbial Pathogenesis*. 2023. Vol. 180. Article 106125. DOI: 10.1016/j.micpath.2023.106125.

42. Asano Y., Hiramoto T., Nishino R., Aiba Y., Kimura T., Yoshihara K., Koga Y., Sudo N. Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice // *American Journal of*

Physiology. Gastrointestinal and Liver Physiology. 2012. Vol. 303, № 11. P. G1288–G1295. DOI: 10.1152/ajpgi.00341.2012.

43. De Vadder F., Kovatcheva-Datchary P., Goncalves D., Vinera J., Zitoun C., Duchampt A. et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits // *Cell*. 2014. Vol. 156, № 1–2. P. 84–96. DOI: 10.1016/j.cell.2013.12.016.

44. Freestone P. P., Haigh R. D., Lyte M. Blockade of catecholamine-induced growth by adrenergic and dopaminergic receptor antagonists in *Escherichia coli* O157:H7, *Salmonella enterica* and *Yersinia enterocolitica* // *BMC Microbiology*. 2007. Vol. 7. Article 8. DOI: 10.1186/1471-2180-7-8.

45. Baker J. M., Al-Nakkash L., Herbst-Kralovetz M. M. Estrogen-gut microbiome axis: physiological and clinical implications // *Maturitas*. 2017. Vol. 103. P. 45–53. DOI: 10.1016/j.maturitas.2017.06.025.

46. Zierer J., Jackson M. A., Kastenmüller G., Mangino M., Long T., Telenti A. et al. The fecal metabolome as a functional readout of the gut microbiome // *Nature Genetics*. 2018. Vol. 50, № 6. P. 790–795. DOI: 10.1038/s41588-018-0135-7.

47. Söderholm J. D., Perdue M. H. Stress and gastrointestinal tract. II. Stress and intestinal barrier function // *American Journal of Physiology. Gastrointestinal and Liver Physiology*. 2001. Vol. 280, № 1. P. G7–G13. DOI: 10.1152/ajpgi.2001.280.1.G7.

48. Niu L., Gao M., Wen S., Wang F., Shangguan H., Guo Z. et al. Effects of catecholamine stress hormones norepinephrine and epinephrine on growth, antimicrobial susceptibility, biofilm formation, and gene expressions of enterotoxigenic *Escherichia coli* // *International Journal of Molecular Sciences*. 2023. Vol. 24, № 21. Article 15646. DOI: 10.3390/ijms242115646.

49. Hegde M., Wood T. K., Jayaraman A. The neuroendocrine hormone norepinephrine increases *Pseudomonas aeruginosa* PA14 virulence through the *las* quorum-sensing pathway // *Applied Microbiology and Biotechnology*. 2009. Vol. 84, № 4. P. 763–776. DOI: 10.1007/s00253-009-2045-1.

50. García-Gómez E., González-Pedrajo B., Camacho-Arroyo I. Role of sex steroid hormones in bacterial-host interactions // *BioMed Research International*. 2013. Vol. 2013. Article 928290. DOI: 10.1155/2013/928290.

51. Org E., Mehrabian M., Parks B. W., Shipkova P., Liu X., Drake T. A., Lusis A. J. Sex differences and hormonal effects on gut microbiota composition in mice // *Gut Microbes*. 2016. Vol. 7, № 4. P. 313–322. DOI: 10.1080/19490976.2016.1203502.

52. Saravinovska K., Santi D., Costantino F., Prete A., Šojat A. S., Spaggiari G. et al. The impact of estrogen status on the gut microbiome: a systematic review and meta-analysis // *Frontiers in Endocrinology*. 2026. Vol. 17. Article 1780806. DOI: 10.3389/fendo.2026.1780806.

53. Kwa M., Hussey G., Novik Y. et al. Evaluation of the gut microbiome and sex hormones in postmenopausal women with newly diagnosed hormone receptor-positive breast cancer versus healthy women: a prospective case-control study // *Journal of Cancer Research and Clinical Oncology*. 2025. Vol. 151. Article 275. DOI: 10.1007/s00432-025-06338-z.

54. Bailey M. T., Dowd S. E., Galley J. D., Hufnagle A. R., Allen R. G., Lyte M. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation // *Brain, Behavior, and Immunity*. 2011. Vol. 25, № 3. P. 397–407. DOI: 10.1016/j.bbi.2010.10.023.

55. Fischer A., Gluth M., Weege F., Pape U. F., Wiedenmann B., Baumgart D. C., Theuring F. Glucocorticoids regulate barrier function and claudin expression in intestinal epithelial cells via MKP-1 // *American Journal of Physiology. Gastrointestinal and Liver Physiology*. 2014. Vol. 306, № 3. P. G218–G228. DOI: 10.1152/ajpgi.00095.2013.

56. Braniste V., Leveque M., Buisson-Brenac C., Bueno L., Fioramonti J., Houdeau E. Oestradiol decreases colonic permeability through oestrogen receptor β-mediated up-regulation of occludin and junctional adhesion molecule-A in epithelial cells // *Journal of Physiology*. 2009. Vol. 587, Pt 13. P. 3317–3328. DOI: 10.1113/jphysiol.2009.169300.

57. Miyata M., Lee J. Y., Susuki-Miyata S., Wang W. Y., Xu H., Kai H. et al. Glucocorticoids suppress inflammation via the upregulation of negative regulator IRAK-M // *Nature Communications*. 2015. Vol. 6. Article 6062. DOI: 10.1038/ncomms7062.

58. Duran-Pinedo A. E., Solbiati J., Frias-Lopez J. The stress hormone cortisol induces virulence in the oral microbiome // *NPJ Biofilms and Microbiomes*. 2018. Vol. 4. Article 25. DOI: 10.1038/s41522-018-0068-z.

59. Калініченко С. В., Рижкова Т. А., Антушева Т. І., Скляр Н. І., Коротких О. О. Метод визначення катаболічної активності мікроорганізмів за кількістю окисленої глюкози // *Вісник проблем біології і медицини*. 2012. Вип. 4, т. 2 (97). С. 150–153.

Information about the authors:
Kalinichenko Svitlana Viktorivna,
https://orcid.org/0000-0002-3482-9605
Doctor of Medical Sciences,
Senior scientific specialist in medicine,
Head of the Laboratory of Viral Infections,
State Institution «I. Mechnikov Institute of Microbiology and Immunology
National Academy of Medical Sciences of Ukraine»
14/16, H. Skovorody Str., Kharkiv, Ukraine

Kordon Tetiana Ivanivna,
https://orcid.org/0000-0001-5813-3656
Candidate of Biological Sciences,
Senior Researcher at the Laboratory of Viral Infections,
State Institution «I. Mechnikov Institute of Microbiology and Immunology
National Academy of Medical Sciences of Ukraine»
14/16, H. Skovorody Str., Kharkiv, Ukraine

Dubinina Natalia Vladyslavivna,
https://orcid.org/0000-0002-0022-6830
Candidate of Medical Sciences, Associate Professor
Associate Professor at the Department of Clinical Laboratory Diagnostics,
Microbiology and Biological Chemistry,
National University of Pharmacy
53, Hryhorii Skovoroda Str., Kharkiv, Ukraine