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BIOLOGICAL FEATURES AND MEDICAL SIGNIFICANCE OF THE *LISTERIA* BACTERIA

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Abstract. Bacteria of the genus *Listeria* are widely distributed in the environment; they are isolated from soil and water ecosystems, food products, environmental objects, and circulate *in vivo*. *L. monocytogenes* are pathogenic for animals and humans. The ecological plasticity, stress resistance and tolerance of *Listeria* determines their ability to switch from a saprophytic to a parasitic life cycle and survive under various environmental conditions. After thawing and subsequent cultivation of *Listeria* on fresh nutrient medium, a pronounced populational heteromorphism is noted: formation of protoplast-type cells, L-forms and convoluted revertant cells, which requires the use PCR and ELISA for bacteria detection. It is known that non-pathogenic *Listeria*, as well as pathogenic microorganisms forming a biocenosis with *L. monocytogenes*, can serve as a reservoir of pathogenicity and resistance determinants and be transferred to pathogenic *Listeria* by horizontal transfer, which leads to the emergence of new, more virulent and antibiotic-resistant strains. In addition, the most important adaptation mechanism of *L. monocytogenes* to adverse environmental factors is their ability to form biofilms markedly enhancing survival and disinfectant resistance. The relatively high genomic similarity between *L. monocytogenes* and some non-pathogenic *Listeria* species and often their coexistence in similar ecological niches, may provide an opportunity for the transfer of resistance or virulence genes. At the same time, the transmission of pathogenicity genes from *L. monocytogenes* to *L. innocua* is also possible, which predetermines the appearance of atypical hemolytic pathogenic strains, which, given the greater environmental prevalence of the latter can pose a great danger to humans and animals. The increasing role of *Listeria* in the pattern of human and animal infectious pathologies, the variability of their morphological, cultivable and biochemical properties, as well as the constant modification of the surface *Listeria* antigens underlies a need to improve listeriosis diagnostics and requires creation of new immunobiological preparations and modern regimens for isolation and identification of various *Listeria* types. This review discusses current views on *Listeria* spp. prevalence and biological qualities, virulence and pathogenicity factors of *L. monocytogenes*, as well as methods for identifying different *Listeria* species.

Key words: *bacteria, Listeria, listeriosis, L. monocytogenes, L. innocua, pathogenicity.*

БИОЛОГИЧЕСКИЕ ОСОБЕННОСТИ И МЕДИЦИНСКАЯ ЗНАЧИМОСТЬ БАКТЕРИЙ РОДА *LISTERIA*

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Резюме. Бактерии рода *Listeria* широко распространены в окружающей среде, выделяются из почвенных и водных экосистем, продуктов питания, объектов внешней среды, циркулируют в организме. Некоторые их виды, прежде всего, *L. monocytogenes*, являются патогенными для человека и животных. Экологическая пластичность, стрессо-

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устойчивость и толерантность листерий обусловливает их способность переходить от сапрофитного к паразитическому образу жизни и снова реверсировать к сапрофитизму при попадании в окружающую среду и выживать при различных ее условиях. При этом выявлено, что после размораживания и последующего культивирования листерий на свежих питательных средах отмечается выраженный гетероморфизм популяции, в том числе образование клеток протопластного типа, L-форм и извитых клеток-ревертантов, что усложняет их обнаружение и типирование в размороженных пищевых продуктах и требует применения таких методов обнаружения бактерий, как ПЦР и ИФА. Известно, что непатогенные листерии, а также патогенные микроорганизмы, образующие биоценоз с *L. monocytogenes*, могут служить резервуаром детерминант патогенности и резистентности и быть переданы патогенным листериям путем горизонтального переноса, что обусловливает появление новых более вирулентных и патогенных, а также резистентных к антибиотикам штаммов. Кроме того, важнейшим механизмом адаптации *L. monocytogenes* к неблагоприятным факторам окружающей среды является их способность к образованию биопленок, существенно повышающих выживаемость и устойчивость к дезинфикантам. Сравнительно высокое геномное сходство между *L. monocytogenes* и некоторыми непатогенными видами листерий, в том числе *L. innocua*, и зачастую их сосуществование в сходных экологических нишах может предоставить возможность для переноса генов устойчивости или вирулентности и обусловливает возможность создания у *L. innocua* резервуаров генов устойчивости, которые могут передаваться бактериям *L. monocytogenes.* В то же время, возможна передача генов патогенности от *L. monocytogenes* к *L. innocua*, что предопределяет появление атипичных гемолитических патогенных штаммов, которые, учитывая более широкое распространеннее *L. innocua* в окружающей среде, могут представлять большую опасность для человека и животных. Увеличение роли листерий в структуре инфекционных патологий человека и животных, изменчивость их морфологических, культуральных и биохимических свойств, а также постоянная модификация поверхностных антигенов листерий предопределяет необходимость совершенствования диагностики листериоза и требует создания новых иммунобиологических препаратов и современных схем для выделения и идентификации различных видов листерий. В настоящем обзоре рассматриваются современные представления относительно распространенности и биологических свойств *Listeria* spp., факторов вирулентности и патогенности *L. monocytogenes*, а также методов идентификации листерий разных видов.

Ключевые слова: *бактерии, листерии, листериоз, L. monocytogenes, L. innocua, патогенность.*

Inroducion

It is known that bacteria of the genus *Listeria* can cause listeriosis, a severe infectious disease of humans and animals characterised by polymorphic clinical manifestations, high mortality (up to 20–40% among adults and more than 50% in newborns) [28] and often complicated by meningoencephalitis [97]. At the same time, while previously only *L. monocytogenes* was considered pathogenic for humans, the literature has recently begun to describe cases of listeriosis infection caused by other *Listeria* species, including *L. ivanovii* [66], *L. seeligeri* [140], *L. innocua* [103], *L. welshimeri* [43], and *L. grayi* [150].

In general, it is currently accepted that *L. monocytogenes* is the etiological agent of listeriosis in humans and many vertebrate species, including birds, whereas *L. ivanovii* causes infections mainly in ruminants [106].

The epidemic situation of listeriosis worldwide continues to worsen due to a number of reasons, including the unique plasticity of *Listeria* and its ability not only to persist but also to multiply in infected products even at low temperatures (+4...+7°C, typical of a refrigerator) [120], acidic environments [124], high salt concentrations [88], and under oxygen-deficient conditions (in vacuum-packed finished products) [45].

At the same time, one unfavourable external factor can increase the resistance of *Listeria* to others. For example, incubation of *L. monocytogenes* at low temperatures was found to increase its resistance to osmotic stress [115]. Similarly, high salt concentrations in the incubation medium can lead to cross-protection of *L. monocytogenes* against other causes of cell death including high temperature, acidity and oxidative stress [128]. It has been revealed that cultivation of *L. monocytogenes* under conditions of vacuum packing and low temperature (+6°C), regardless of the nutrient substrate, causes the formation of a capsule in the pathogen and the emergence of resistance to some antibiotics from the penicillin group [41]. In addition, under unfavourable conditions, *Listeria* are capable of forming biofilms that attach to abiotic or biological surfaces and serve as a survival strategy for the bacteria, allowing them to persist in unfavourable conditions, being protected from the human immune system and various environmental factors (ultraviolet light, acids, drying, salinity, antimicrobial agents, disinfectants) [46].

The extremely high tolerance of *L. monocytogenes* to stress conditions causes a serious problem of listeriosis in the food industry, and the increasing role of *Listeria* in the structure of infectious pathologies of humans and animals predetermines the need to improve the diagnosis, prevention and sanitary and epidemiological surveillance of listeriosis, which requires the creation of new immunobiological preparations and modern schemes for the isolation and identification of various *Listeria* species.

The present review discusses the current understanding of the prevalence and biological properties

of *Listeria* spp. and the virulence and pathogenicity factors of *L. monocytogenes*, as well as methods of identification of *Listeria* species.

The prevalence and biological properties of species of the *Listeria* genus

Listeria spp. are gram-positive flagellated bacilliform bacteria, facultative anaerobes that do not form spores and are motile at low temperatures [68], are widely distributed in the environment, isolated from soil and aquatic ecosystems, food, and environmental objects, circulate in the body, and some of their species are pathogenic for humans and animals [137].

Initially (until 2009), 7 species were identified in the genus *Listeria* (Pirie, 1940): *L. monocytogenes*, *L. ivanovii*, *L. grayi*, *L. murrayi*, *L. innocua*, *L. seeligeri*, and *L. welshimeri*, of which *L. monocytogenes*, the main causative agent of listeriosis, poses the greatest threat to humans. In the last decade, due to the rapid development of sequencing technologies, 13 new species with diverse phenotypic and genotypic characteristics have been identified within the genus *Listeria*: *L. marthii* [83], *L. rocourtiae* [100], *L. fleischmannii* [47], *L. weihenstephanensis* [99], *L. riparia* [64], *L. grandensis* [64], *L. floridensis* [64], *L. cornellensis* [64], *L. aquatica* [64], *L. newyorkensis* [141], *L. booriae* [141], *L. costaricensis* [123] and *L. goaensis* [68]. In addition, two subspecies, subsp. *fleischmannii* and subsp. *colouradonensis*, have been established within the species *L. fleischmannii* [65].

Phylogenetic studies based on the 16S and 23S rRNA sequences revealed that the genus *Listeria* includes two evolutionarily formed lineages: *Listeria* sensu strictu, which includes *L. monocytogenes*, *L. innocua*, *L. welshimeri*, *L. seeligeri*, *L. ivanovii*, and *L. marthii*, and *Listeria* sensu lato, which unites *L. grayi*, previously considered nonpathogenic, and 12 new *Listeria* species discovered since 2009 [58, 126]. All 6 species of *Listeria* sensu strictu share common phenotypic characteristics, such as the ability to grow at low temperatures and flagellar motility, whereas the 11 species of *Listeria* sensu lato represent three distinct monophyletic groups that can be recognised as separate genera [126]. These three putative genera of *Listeria* are immobile (except *L. grayi*), capable of nitrate reduction (except *L. floridensis*) and give a negative result in the Voges–Proskauer test (except *L. grayi*) [126]. Unlike all other *Listeria* species, species of the proposed new genus *Mesolisteria* cannot grow at temperatures below 7°C [126].

The prevalence of *Listeria* in the environment

The main source and reservoir of *Listeria* are environmental objects, primarily soil. *Listeria* is also excreted from plants, silage, dust, water bodies and sewage [26]. There are 92 known animal species that serve as reservoirs or participate in the circulation of *Listeria*. The spread of the pathogen is particularly intensive during the period of rodent migration to places of their concentration (haystacks, hayfields). Rodents play a leading role in the transmission of *Listeria* to farm animals by contaminating feed and water [22]. Transmission of the pathogen between rodents in natural foci is supported by arthropods, including mites.

In addition, *Listeria* can be present in water in the environment, and therefore infection of animals through water is possible [33], including live fish, on whose body surface *Listeria* can multiply using the esculin of the mucus covering the scales as a food source [25]; cold smoking of fish creates specific conditions (salt, smoking solution) that favour *Listeria* multiplication [85]. *Listeria* can multiply in water and in soil microecosystems at low temperature with preservation of virulence of populations [37], which determines the spread and long-term persistence of *Listeria* in the external environment and economic objects.

Ecological plasticity and tolerance of *Listeria* stipulates their ability to switch from saprophytic to parasitic lifestyle and to reverse to saprophyticism again when introduced into the environment and survive under its various conditions. *Listeria* concentration has been found to increase in the external environment in autumn and spring, stabilise in winter and decrease in summer [7]. In addition, the ability of *Listeria* to actively multiply in melt water (at a temperature of 6°C) has been revealed, providing a 2-fold increase in bacterial mass [7]. At the same time, no significant changes in cell morphology in the population were observed when *Listeria* survived at low temperatures, including sub-zero temperatures, but after thawing and subsequent cultivation on fresh nutrient media, a pronounced heteromorphism of the *Listeria* population was observed, including the formation of protoplast-type cells, L-forms, and twisted revertant cells [5]. In this regard, the detection of *Listeria* in unfrozen food products requires, firstly, a long time for reversion in enrichment medium, and, secondly, there is a need to apply bacterial detection methods such as DNA diagnosis, PCR and ELISA.

The ability of *Listeria* to remain viable on food-contact surfaces in packinghouses has been revealed, which predetermines the likelihood of contamination of food products, including fruit, with a subsequent increase in the abundance of these bacteria as the products are stored [141]. In addition, there has recently been a steady increase in the proportion of multiple antibiotic-resistant *L. monocytogenes* strains worldwide [44], with additional pathogenicity factors [18].

In addition to abiotic factors, *Listeria* biology is also influenced by biotic environmental factors, including saprophytic microorganisms that contaminate food products, form common biocenoses with *Listeria*, and influence *Listeria* through exogenous

metabolites or competition for nutrient substrates [36]. Nonpathogenic *Listeria*, as well as pathogenic microorganisms that form a biocenosis with *L. monocytogenes*, can serve as a reservoir of pathogenicity and resistance determinants and can be transmitted to pathogenic *Listeria* by horizontal transfer [9].

L. monocytogenes and *L. innocua* are the most common species of the genus *Listeria*, related in a strict sense [94] and often co-exist in environmental sites. It was initially hypothesised that the two species evolved from a common ancestor but differ due to the loss of virulence genes in *L. innocua* [55]. It was later hypothesised that *L. innocua* evolved from the ancestors of four strains of the *L. monocytogenes* serogroup and may have retained some characteristics of its ancestor [116]. Atypical *L. innocua* was found to induce a protective immune response against *L. monocytogenes*, which is also in favour of a close genetic relationship between *L. innocua* and *L. monocytogenes* [111].

Genetically close to these two species is *L. welshimeri*, which is characterised by a smaller genome size compared to *L. monocytogenes*, suggesting similar evolutionary pathways of their genomes from a common ancestor [86]. However, the genome of the ancestor of *L. welshimeri* was more compact than that of *L. monocytogenes*, which led to the emergence of non-pathogenic species of *Listeria* spp. [86]. At the same time, the *prfA* virulence gene cluster present in the common ancestor of *Listeria* species was eventually lost in *L. innocua* and *L. welshimeri* [94, 116].

The bacteria of *L. welshimeri* species are found in meat products and *L. seeligeri* in fish [17]. *L. innocua* is the predominant species in seawater, especially in coastal waters, compared to other *Listeria* species, which may cause contamination of fish, squid, crustaceans and other animals (seafood) and pose a risk to humans [74]. Bacteria of this species are often found in meat (frozen minced meat and semi-finished products, as well as smoked products ready for consumption), fish (salted, raw smoked fish, chilled and frozen semi-finished products), vegetables (onions, cabbage, potatoes, beetroot) stored in vegetable warehouses [17, 73], and are capable of adaptation in changing environmental conditions (survival in a wide range of temperature, humidity, pH of the environment), which significantly increases their chances of survival in different environmental conditions, causes their widespread active distribution and promotes the emergence of strains with atypical properties [59]. Thus, in addition to food products, *L. innocua* species are often present in silage and organs of rodents [17]. *L. innocua* have dual nature and are capable of both saprophytic and parasitic lifestyle depending on the habitat [15].

Bacteria of *L. monocytogenes* species were first isolated and described in 1911 by the Swedish scientist G. Hulphers from purulent pus. Hulphers from a purulent nodule of the liver of a fallen rabbit [93], and a precise and detailed description of listeriosis was made in 1923 by E. Murray et al. [119]. The first documented culture of the pathogen in humans was isolated in France in 1921 by Dumont and Cotoni from a patient with meningitis, and its modern name was given in 1940 in honour of the English surgeon J. Lister, the founder of antiseptic methods. Despite the fact that *L. monocytogenes* is the main causative agent of listeriosis in humans, it is typical of the normal microflora of the middle and lower intestinal tracts of many animal and human species [54]; therefore, it may be excreted with faeces into the environment and subsequently contaminate soil, water, grass, etc.

The relatively high genomic similarity between *L. innocua* and *L. monocytogenes*, and sometimes their coexistence in similar ecological niches, may provide an opportunity for horizontal transfer of resistance or virulence genes [102]. And, in particular, although antimicrobial resistance is less common in *L. monocytogenes* than in *L. innocua*, but *L. innocua* may form a reservoir of resistance genes that can be transferred between bacterial species, including transferring them to pathogenic *L. monocytogenes* [81]. In addition, the possibility of transferring antibiotic resistance genes to *Listeria* spp. from enterococci via transposons is also accepted [92].

Biological properties of *L. monocytogenes, L. innocua* and *L. ivanovii*

Morphologically, *L. monocytogenes*, *L. innocua* and *L. ivanovii* are short, gram-positive, non-spore-forming bacilli of regular shape and are facultative anaerobes [26]. However, *L. monocytogenes* and *L. ivanovii* can transform into L-forms and parasitise intracellularly [26], showing the ability to survive in macrophages and infiltrate a number of normally non-phagocytic cells such as epithelial cells, hepatocytes and endothelial cells [139].

L. monocytogenes exhibits the ability to grow in a wide range of temperatures (1–45°C, with the optimum temperature for their growth being 30–37°C) and pH (from 4.0–4.8 to 9.5–10.0) in the presence of NaCl (20%) and 15% CO_2 [11]. At 70°C, *Listeria* die within half an hour and at 100°C within 3–5 minutes [34].

L. monocytogenes is able to remain viable when stored in semi-liquid nutrient medium and lyophilised under refrigerator conditions [4]. In this regard, dairy products with a long shelf life, including soft cheeses, ice cream and butter, are the most dangerous source of listeriosis, as they multiply at low temperatures and accumulate dangerous doses of *Listeria* in milk [18]. In addition, *L. monocytogenes* is detected not only in raw products, but also in cooked, uncooked and raw smoked meat products, frozen, pickled and preserved seafood, as well as various semi-finished products [144].

The high thermostability of *Listeria* is due to the presence of a complex of genetic and biochemical mechanisms that allow them to adapt to changing temperature conditions and survive in many environmental objects. One of the mechanisms of thermoadaptation is the induction and repression of genes acting at the isoenzyme level, regulating the launch of synthesis of "cold" and "heat" isoenzymes. Moreover, the number of "cold" isoenzymes in *Listeria* significantly exceeds the number of "thermal" isoenzymes, which makes *Listeria* facultative psychrophiles. The most important mechanism of adaptation of *Listeria* to unfavourable environmental factors is their ability to form biofilms, which significantly increase survival and resistance to disinfectants [134].

The wide range of host organisms in which *L. monocytogenes* can reproduce has caused antigenic heterogeneity of its outer envelope [23]. Thus, using molecular typing methods, it is possible to distinguish within the species of *L. monocytogenes*, three evolutionary lineages can be distinguished within the *L. monocytogenes* species, characterised by different pathogenic potentials: Lineage I are strains associated with epidemic outbreaks of listeriosis (serotypes 1/2b, 3b, 4b, 4d and 4e); Lineage II are strains isolated during sporadic cases of listeriosis (serotypes 1/2a, 1/2c, 3a and 3c); Lineage III are strains rarely associated with cases of listeriosis (serotypes 4a and 4c) and Lineage IV (4a, 4b, 4c) [107, 126, 131]. The most common serotypes of *L. monocytogenes* in listeriosis patients are 4b, 1/2a, 1/2b [14]. At the same time, about half of all cases of listeriosis in the world are caused by strains of serovar 4b, whereas serovariants 1/2a, 1/2b, 1/2c, and 3a are most often detected in infected products and natural environment [58, 104, 105].

At the same time, no regularities between the biological type of the host and the serovars of the isolated strains or the severity of the disease have been found. At the same time, it has been established that the course of the pathological process and host specificity are determined by listeriolysin and internalins A and B, which act as pathogenicity factors of *Listeria* [38, 126]. It has been found that DNA regions encoding *Listeria* pathogenicity factors are more frequently found in strains of serovar 4b [118].

Intraspecific cross-reactions are characteristic of *Listeria*: in particular, a culture containing DNA fragments characteristic of other serovariants was isolated within serovariant 4b [101]. In addition to intraspecies cross-reactions, *Listeria* also cross-reacts serologically with typhoid-paratyphoid bacteria and staphylococci [10].

The most genetically similar species to *L. monocytogenes* is *L. innocua*, which serves as an indicator of the possible presence of *L. monocytogenes* in products and can be pathogenic not only to animals [139], but also to humans [117].

The bacteria of *L. innocua* species are characterised by stability of phenotypic manifestations: morphology (short, randomly arranged bacilli, coccoid forms and ovoid bacteria that stain positively according to Gram stain), blue or bluish-green luminescence in oblique light, typical growth of colonies on nutrient media with a characteristic fermented milk odour, presence of catalase and absence of oxidase activity, motility at temperatures of 22°C and 37°C. Bacteria of this species are catalase-positive, most cultures show DNAase activity, and some strains are characterised by haemolytic activity [15]. In addition, bacteria of the *L. innocua* species are characterised by the presence of a gene encoding lecithinase, typical of *L. monocytogenes* [82], but not typical of *L. monocytogenes*, which retains lecithinase activity when cultured on nutrient medium containing lecithin, both in the presence and absence of activated carbon [21]. *L. innocua* is sensitive to penicillins, aminoglycosides, carbapenems, fluoroquinolones, but resistant to nalidixic acid [15].

A peculiarity of *L. innocua* is the variability of biochemical activity. Thus, some experts [15] have established the ability of *L. innocua* to degrade glucose, salicin, rhamnose, mannose, maltose, esculin and fructose, along with the absence of degradation of urea, dulcite, inulin, adonite, raffinose, melibiose, starch and arabinose. The study of pathogenicity factors in some cultures of *L. innocua*, especially those isolated from fish, revealed haemolytic activity uncharacteristic for bacteria of this species [15], indicating the appearance of atypical strains and possibly due to the appearance of gene clusters similar to *L. monocytogenes* in the genome of *L. innocua* [59].

Although *L. monocytogenes* and *L. innocua* differ markedly in virulence, they are virtually indistinguishable by classical taxonomic criteria. Both species are actively motile and produce flagellin abundantly at 22°C. However, these species differ in motility and flagellin production at 37°C. At this temperature, *L. monocytogenes* strains are virtually immobile and produce little or no flagellin, whereas *L. innocua* strains are often motile and produce significant amounts of flagellin [95]. These data point in favour of differential regulation of flagellin production in *L. monocytogenes* and *L. innocua* at 37°C.

L. monocytogenes strains are characterised by the presence of both somatic O and flagellar H-antigens, whereas *L. ivanovii* (serotype 5) and *L. innocua* (serotype 6) have only one somatic O-antigen each [42].

Biological properties of other *Listeria* species

Phenotypic properties of other species of the genus *Listeria*: *L. ivanovii*, *L. grayi*, *L. murrayi*, *L. seeligeri*, *L. welshimeri* are not sufficiently defined, and in some respects are similar to *L. monocytogenes* bacteria, which may lead to inaccurate identification. Thus, it is known that the new *Listeria* species do not differ from *L. monocytogenes* and are short ba-

cilli of regular shape with rounded ends, sometimes almost cocci, gram-positive, capsules and spores do not form, they are not resistant to acid, aerobes, facultative anaerobes, chemoorganoautotrophs, but in the external environment are chemolithoautotrophs, catalase-positive, oxidase-negative, exhibit motility at 20–25°C [8].

Bacteria of *L. marthii* species grow well on conventional nutrient media in the temperature range of 1–45°C, the optimal temperature is 30–37°C. They are motile, form an umbrella of 3–5 mm in semi-liquid agar at 20–30°C and do not form it at 37°C. Nonhemolytic, hydrolyse esculin, produce hydrogen sulfide, tolerant to sodium chloride, positive for methyl red, ferment D-glucose, lactose and maltose; do not ferment D-xylose, D-mannite, sucrose and L-rhamnose, reduce nitrates, active against urease, form indole and hydrolyse gelatin. On dense media, after incubation for 24 hours at 37°C, colonies 0.2–0.8 mm in diameter, smooth, bluish-green, translucent, slightly raised with a fine surface texture and a smooth edge grow. The type strain is FSL S4-120T [83].

Colonies of *L. rocourtiae* species after 48 h of cultivation at 30°C grow on trypticase-soya agar 0.5–1.0 mm in diameter, round, translucent, convex with a fine surface texture and a smooth edge. They reduce nitrate and manite, do not exhibit haemolytic activity, are able to degrade to acid ribose, D-xylose, galactose, glycerol, erythritol, adonite, D-glucose, D-fructose, D-mannose, L-sorbose, rhamnose, dulcite, inositol, mannitol, sorbitol, methyl-D-glucoside, N-acetylglucosamine, amygdalin, arbutin, salicin, cellobiose, maltose, lactose, melibiose, starch, trehalose, glycogen and D-raffinose. It does not ferment L-xylose, D-arabinose, L-arabinose, methyl-D-mannoside, sucrose, inulin, melecitose, L-fructose, xylitol, D-turanose, D-fructose, D-tagatose, D-arabitol, 5-ketogluconate or 2-ketogluconate. The type strain is CIP 109804 (DSM 22097) [100].

The bacteria of *L. fleischmannii* species are typical short bacilli arranged singly or in short chains (0.4–0.6 mm diameter and 0.7–1.2 mm length). On nutrient agar at 37°C after 24 hours, colonies grow 0.4–1.0 mm in diameter, translucent, round, with a low convex surface and smooth edges. Immobile, although they contain the flagellin *flaA* gene. Reduce nitrate, hydrolyse hippurate and esculin, and produce hydrogen sulphide. The main differentiating character that distinguishes this species from others is the unique ability to ferment D-mannite and D-xylose. The species *L. fleischmannii* is non-haemolytic, does not invade Caco-2 cells and does not contain *Listeria* virulence genes on pathogenic islet 1. The type strain is LU2006-1T (DSM 24998) [47]. Based on molecular genetic studies, the species *L. fleischmanni* was divided into subspecies according to genomic characteristics: *L. fleischmannii* subsp. *fleischmannii* and *L. fleischmannii* subsp. *colouradonensis* [65].

Bacteria of the subspecies *L. fleischmannii* subsp. *fleischmannii* are characterised by an optimal growth temperature of 30–37°C, are immobile at 25°C, are non-haemolytic, reduce nitrate, and degrade D-xylose to acid, D-arabitol, L-rhamnose, α-methyl-D-glucoside, D-ribose, turanose, sucrose and melecitose, and do not ferment glucose-1-phosphate, inositol, arylamidase, α-mannosidase and D-tagatose. The typical strain is LU2006-1 [65].

Bacteria of the subspecies *L. fleischmannii* subsp. *soloradonensis* are characterised by similar phenotypic features to the subspecies *L. fleischmannii* subsp. *fleischmannii*, but differ from it in their inability to ferment sucrose, melecitose, and turanose, but ferment inositol. The type strain is TTU M1-001 [47, 65]. The genomes of both subspecies of *Listeria fleischmannii* contain putative enhancin genes; a mosquitocidal toxin has been identified in the genome of *Listeria fleischmannii* subsp. *colouradonensis*, suggesting possible adaptation to insect habitation [47, 65].

Bacteria of *L. weihenstephanensis* species are non-haemolytic bacilli 0.4–0.5 mm in diameter and 2.0–4.5 mm in length with rounded ends; colonies 1.0–2.5 mm in diameter, translucent, whitish, round, smooth, slightly convex with slightly irregular edges grow on trypticase-soya agar. The optimum temperature for their growth is 28–34°C, they do not grow at 38°C, their mobility is weak at 15–30°C, the optimum pH is 7–8. Isolates can grow in broth at 3°C for 10 days in anaerobic conditions. They grow well in nutrient broth containing 6.5% NaCl. Test positive with methyl red, negative with Voges–Proskauer and CAMP test, do not hydrolyse urea and do not form indole and hydrogen sulphide, reduce nitrate to nitrite. Do not ferment α-mannosidase, arylamidase, D-ribose, 1-phosphate-glucose and D-tagatose. Esculin, D-arabitol, D-xylose, L-rhamnose and methyl-D-glucopyranoside are fermented [99]. After 14 days of anaerobic incubation, acid formation is noted from glycerol, D-ribose, D-xylose, D-glucose, D-fructose, D-mannose, L-rhamnose, inositol, D-mannite, and methyl-D-glucopyranoside, N-acetylglucosamine, amygdalin, arbutin, aequulin, salicin, cellobiose, maltose, lactose, trehalose, starch, glycogen, xylitol, gentiobiose, D-arabitol and potassium 5-ketogluconate. Not able to degrade erythritol, D-arabinose, L-arabinose, D-galactose, L-xylose, D-adonite, L-sorbose, methyl-b-D-xylopyranoside, dulcite, D-sorbitol, methyl-D-mannopyranoside to acid, melibiose, sucrose, inulin, melecytose, raffinose, turanose, D-lyxose, D-tagatose, D-fucose, L-fucose, L-arabitol, potassium 2-ketogluconate and potassium gluconate [99].

Bacteria of *L. floridensis* species are morphologically bacilli with rounded ends, 0.6 × 1.3–1.9 mm in size, unable to grow at temperatures below 7°C. The optimum temperature for their growth is 37–41°C; they do not show motility at temperatures of 4, 22, 30 and 37°C. The species *L. floridensis* is the only species of the genus *Listeria* lacking motility and

unable to reduce nitrate, characterised by negative Voges–Proskauer reaction and CAMP test. The typical strain is FSL S10-1187 [64].

The bacteria of *L. aquatica* species are 0.6–0.7 × 1.5–2.4 mm in size, like *L. floridensis* are unable to grow at temperatures below 7°C, and the optimal temperature for them is 37–41°C, are not motile at 4, 22, 30 and 37°C, and show negative Voges–Proskauer reaction and CAMP test. Unlike *L. floridensis*, they reduce nitrate but do not reduce nitrite, do not ferment maltose but are able to ferment D-tagatose. The typical strain is FSL S10–1188 [64].

Bacteria of *L. riparia* species are straight bacilli with rounded ends, measuring 0.5–0.7 × 2.3–3.7 mm. Like *L. floridensis* and *L. aquatica*, they do not grow at 7°C and below, their optimum temperature is 37–41°C, are not motile at 4, 22, 30 and 37°C, and show negative Voges–Proskauer reaction and CAMP test. Similar to L. aquatica and unlike *L. floridensis*, they reduce nitrate and do not reduce nitrite. The main differential characteristic from other species of the genus *Listeria* is the ability to ferment L-rhamnose, mannose, D-galactose and L-arabinose. The typical strain is FSL S10–1204 [64].

The species *L. cornellensis* is represented by straight sticks with rounded ends, measuring 0.4–0.7 × 2.4–3.8 mm. The optimum temperature for their growth is 30–37°C, they are not motile at 4, 22, 30 and 37°C, exhibit negative Voges–Proskauer reaction and CAMP test. They reduce nitrate and do not reduce nitrite. Phenotypic traits resemble the species *L. grandensis*. The typical strain is TTU A1-0210 [64].

Phenotypically similar to *L. cornellensis* are bacteria of *L. grandensis* species, which morphologically are straight bacilli with rounded ends, 0.6–0.7 × 2.0–3.1 mm in size. Their optimum growth temperature is 30–37°C, and they are immobile at temperatures of 4, 22, 30 and 37°C. Voges–Proskauer reaction and CAMP test are negative. Reduces nitrate and does not reduce nitrite. The type strain is TTU A1–0212 [64]. In addition, *L. cornellensis* and *L. grandensis* are the only species of *Lisretia* unable to cleave L-rhamnose. At the same time, *L. cornellensis* differs from *L. grandensis* species in its weak lactose cleavage [64].

Bacteria of *L. newyorkensis* species are immobile at all temperatures, able to grow in the temperature range of 4–41°C, the optimal temperature for their growth is 30–37°C. Able to reduce nitrate but do not ferment nitrite. Show positive reaction with methyl red, Voges–Proskauer test negative, unable to ferment xylitol, D-fructose, α-mannosidase, D-arabitol, but do ferment D-galactose, D-ribose and L-arabinose. The typical strain is FSL M6-0635 [152].

Bacteria of the species *L. booriae* are non-haemolytic bacilli, non-motile at all temperatures and capable of growth between 4–41°C, the optimum temperature for growth is 30–41°C. They differ from other species in their ability to ferment D-arabitol, melibiose and L-arabinose. The typical strain is FSL A5-0281 [152].

The species *L. costaricensis* shows the greatest similarity in the structure of 16S rRNA genes with the type strain *L. floridensis* (98.7%), which allowed us to assign it to the same branch as *L. fleishmannii*, *L. floridensis* and *Listeria* sensu lato. The typical strain is CLIP 2016/00682 [123].

L. goaensis are short non-spore-forming gram-positive immobile bacilli, oxidase-negative, catalase-positive and exhibit the ability to α-haemolysis on dishes with 5% agar with sheep and horse blood [68].

Thus, bacteria of the genus *Listeria* are ubiquitous and have a wide adaptive capacity that allows them to adapt to existence in different environments and, at the same time, to acquire various uncharacteristic properties. In this regard, knowledge of phenotypic features of biological properties of different *Listeria* species may be useful in determining approaches to the detection of epidemically dangerous *Listeria* from a variety of environmental objects.

Pathogenicity factors of *L. monocytogenes*

Currently, *L. monocytogenes* serves as a model system for studying the main aspects of intracellular pathogenesis, as its ability to parasitise in the cytosol of mammalian cells, to use the actin-based motility system and to spread from cell to cell, avoiding contact with the humoral immune system [150], to overcome three principal protective barriers on the way of spreading in the body has been established: to penetrate through intestinal enterocytes, entering the blood and lymph, and to overcome the blood-brain barrier and placental barrier [63]. At the same time, *L. monocytogenes* is able to penetrate into target cells by phagocytosis, including it in those cells for which it is not characteristic, and, as a result, to affect various cell types, suppressing at the initial stages of infection the Th1-type immune response, which is the main one for the elimination of intracellular parasites, which significantly complicates the organism's fight against this pathogen [1].

The most typical features of *L. monocytogenes* are an exceptionally large number of surface proteins, an abundance of transport proteins, in particular proteins designed for carbohydrate transport, and a variety of regulatory proteins [50].

Surface proteins play an important role in the interactions of the microorganism with the environment, including target cells during infection of the host organism. In this case, the main virulence factors of *L. monocytogenes* are such surface proteins as internalins A and B, necessary for penetration into eukaryotic cells, and *actA*, which plays a key role in actin-based motility [50].

Pathogenicity islands identified in the *L. monocytogenes* genome are LIPI-1 *(prfA, hly, plcA, plcB, mpl* and *actA)* regulated by the PrfA protein [78], LIPI-2 (inlABCJ) [151], LIPI-3 (llsAXAXGHHBYDP) [57] and LIPI-4 (licABC, lm900558-70013

and glvA) [154]. It has been found that the presence of the pathogenicity island LIPI-3 in the genome of the bacterium causes a high level of its virulence and is often accompanied by the development of the meningoencephalic form of the disease [3].

The pathogenesis of *L. monocytogenes* requires the coordinated expression of six genes, namely *prfA, plcA, hly, mpl, actA* and *plcB*, which are mainly localised to the pathogenicity island LIPI-1 [150] regulated by the transcription regulator PrfA [56]. The processes activated by PrfA are crucial for the infection cycle of *L. monocytogenes*. They include phagosome lysis with release of bacteria into the cytoplasm and actin-dependent intercellular mobility of bacteria [77]. For example, the *prfA* gene encodes the transcription activator *prfA*, which directly or indirectly induces the transcription of more than 140 genes, including the other five genes found in LIPI-1 [129]. The *plcA* and *plcB* genes encode phospholipases C, which in combination with listeriolysin O (LLO) protect bacteria from cytoplasmic phagosomes [143]. The *mpl* gene encodes a zinc-metalloprotease required for pro-plcB maturation [134], and the *actA* gene product is a multifunctional virulence factor [149].

Auxiliary, or minor, virulence factors of *L. monocytogenes* are the products of 13 genes, 5 of which are associated with bacterial adhesion to and/or invasion into mammalian cells. The *iap* (invasion-a-associated p protein) gene encodes the extracellular protein p60, which has murein hydrolase activity and is required for bacterial division and invasion into target cells [150]. The *lpeA* gene encodes a protein that belongs to the lipoprotein receptor associated antigen I (LraI) superfamily. LraI proteins, in turn, are associated with the bacterial surface and include several adhesion proteins of many gram-positive pathogenic bacteria, such as the adhesins PsaA, also typical of *Streptococcus pneumoniae*, FimA, typical of *Streptococcus parasanguinis*, and EfmA, also characteristic of *Enterococcus faecium* [110]. The *lpeA* gene also encodes the extracellular domain of SBP ("Streptococcal solute binding proteins"), which in *L. monocytogenes* binds Zn^{2+} and Mn^{2+} and mediates entry into eukaryotic cells, including hepatocytes and macrophages [135].

The *lpsA* gene encodes a protein of the same name, which is a type II signal peptidase required for *lpeA* maturation [136], with genetic defects in *lpsA* causing improper maturation of *lpeA*, subsequent loss of its proper surface localisation and ultimately a significant weakening of *L. monocytogenes* virulence.

The *lap* gene encoding a protein of the same name (*Listeria* adhesion protein p) promotes adhesion to intestinal epithelial cells and facilitates extraintestinal dissemination of bacteria [51]. Specifically, the lap gene product interacts with its cognate host cell receptor, heat shock protein 60 (Hsp60) on the apical side and causes dysfunction of the epithelial barrier, which favours translocation of *L. monocytogenes* across it [71]. Lap is an alcohol acetaldehyde dehydrogenase (lmo1634) present in both pathogenic and non-pathogenic *Listeria* species [91]. However, *lap* exhibits virulent properties only in pathogenic *Listeria* due to the lack of secretion and surface reassociation of *lap* in non-pathogenic species [52, 91]. The interaction of *lap* with the host cell receptor Hsp60 leads to activation and nuclear translocation of nuclear factor-κB (NF-κB), which causes activation of myosin light chain kinase (MLCK) [71]. Activated MLCK phosphorylates myosin light chain (MLC), which predisposes cellular redistribution of tight junction proteins (claudin-1 and occludin) and adhesive junction protein (E-cadherin) and opening of the intercellular junction [71]. Consequently, *L. monocytogenes* performs efficient translocation across the intestinal barrier by activating the Lap-Hsp60-NF-κB-MLCK axis [70].

The *fbpA* gene encodes an adhesin containing fibronectin-binding domains; this protein provides adhesion to target cells, especially hepatocytes [127].

The genome of *L. monocytogenes* also contains genes encoding enzymes that protect bacteria from the host immune system or increase their survival in the cytosol of infected cells. For example, the *pdgA* and *oatA* genes (peptidoglycan-N-deacetylase and O-acetylase, respectively) may be required for resistance to host lysozyme. Mutations in these two genes result in increased sensitivity of peptidoglycan to lysozyme inducing attenuation of *L. monocytogenes* virulence [133].

The *lplA1* gene encodes a lipoatligase that promotes cytosolic replication of *Listeria* in target cells [96].

The *gtcA* gene encodes an enzyme that catalyses glycosylation of teichoic acid in the envelope of *L. monocytogenes*, which mediates key features of pathogenicity: proper anchoring of the main surface virulence factors (Ami and InlB); resistance to antimicrobial peptides and reduced susceptibility to antibiotics [114].

The *prsA2* gene encodes a peptidylprolyl-cis-trans isomerase that promotes proper protein folding, which is essential for the maturation and secretion of some proprotein virulence factors (such as phospholipase C PC-PLC) of *L. monocytogenes*, and the *lplA1* gene is required for intracellular survival of *Listeria* [76].

The c*lpC, clpE* and *clpP* genes encode proteases that presumably act as mediators of the stress response and promote intracellular replication [150].

Hypervirulent isolates of *L. monocytogenes*, in addition to the pathogenicity islet LIPI-1, also contain islets LIPI-3 and LIPI-4 [112]. Moreover, the LIPI-3 islet contains genes encoding listeriolysin S, a second haemolysin that enhances *L. monocytogenes* survival in polymorphonuclear neutrophils, whereas LIPI-4 encodes a cellobiose phosphotransferase system [61] that enhances invasion into the central nervous system, along with maternal-neonatal infection. In ad-

dition, the pathogenicity islet LIPI-3 contains genes encoding important virulence factors, namely internalins. These include the operon InLab, which promotes invasion of epithelial and other cells, and *inlC*, which is involved in intercellular spread [60]. Hypervirulent strains of *L. monocytogenes* containing LIPI-3, having a bactericidal function, have been found to promote intestinal colonisation and can modulate the host microbiota [132].

Along with genes encoding pathogenicity and virulence factors, the genome of *L. monocytogenes* is characterised by the presence of SSI-1 (lmo0444, lmo0445, pva, gadD1 and gadT1) [130] and SSI-2 (lin0464 and lin0465) stress tolerance islands [87]. It was found that SSI-1 predetermines bacterial resistance to acids, salts, and growth in food [130], whereas SSI-2 predetermines survival under alkaline conditions and oxidative stress [57, 87].

It has also been shown that the presence in the *L. monocytogenes* genome of the *lin* gene correlates with resistance to the macrolide clarithromycin, the *sul* gene — to the sulfonamide biseptol, the *fosX* gene — to fosfomycin, the *aad, ant*, and *aph* genes — to amikacin, and alleles 1, 8, 15, 18, and 28 of the *pbp*-like gene — to beta-lactams [3].

An important specific feature of the genomes of the genus *Listeria*, probably also related to the ability of these bacteria to colonise a wide range of ecosystems, is the presence of a large number of genes encoding various transport proteins [50]. As in most bacterial genomes, the predominant class of transport proteins in *Listeria* is ABC-transporters. Moreover, 26% of the genes encoding *Listeria* transport proteins are responsible for carbohydrate transport mediated by the phosphoenolpyruvate-dependent phosphotransferase (PTS) system, which allows bacteria to utilise different carbon sources. Furthermore, in many bacteria studied so far, PTS is a key link between metabolism and regulation of catabolic operons [146].

Thus, the genome of *L. monocytogenes* is characterised by the presence of a large variety of genes responsible for invasion into target cells of the host organism, survival in them, resistance to antibiotics and disinfectants, which determines the high pathogenicity and virulence of bacteria of this species.

Methods of identification of different *Listeria* species

The increasing role of *Listeria* in the structure of human infectious pathologies makes it necessary to improve the diagnosis, prevention, and sanitary and epidemiological surveillance of listeriosis, which predetermines the creation of new immunobiological preparations and modern schemes for the isolation and identification of *L. monocytogenes* in accordance with international standards [30]. In addition, it has been established that *L. monocytogenes* is characterised by variability in morphological, cultural and biochemical properties, which causes difficulties in the laboratory diagnosis of listeriosis. In particular, it has been revealed that storage of food products at +22°C and seafood and dairy products at +6°C may change the pathogenic properties of *Listeria* and, in particular, the loss of haemolytic activity and decreased production of lecithinase, which is important for the differentiation of *L. monocytogenes* from other non-pathogenic *Listeria* species [41].

Currently, morphological, bacteriological, biochemical, serological and molecular biological methods are used to diagnose listeriosis.

Morphological diagnosis of listeriosis is based on the detection during autopsy of granulomas (listeriomas) in internal organs in the form of whitish, greyish or yellowish nodules ranging in size from a poppy seed to a millet grain, which are most often found in the liver, colon, pharynx, oesophagus, lungs, spleen and brain [26]. In the initial stages, listeriomas represent a small focus of inflammation, in the centre of which a large number of partially phagocytised *Listeria* are found among decaying leukocytes. Further the number of leucocytes in the focus increases, and in its peripheral parts an admixture of fibrin is found. At later stages of the process on the periphery of the focus there are small overgrowths of granulation tissue, consisting mainly of macrophages, which can gradually completely replace the area of necrosis. *Listeria* is practically undetectable in the granulation tissue [153].

The biochemical methods of *L. monocytogenes* differentiation are based on catalase positivity, motility at 18–25°C and immobility at 37°C, the ability to hydrolyse esculin and not to exhibit lecithinase activity, typical of *Listeria* parasitising inside the cell, when cultured on nutrient media containing lecithin [21].

The presence of the gene encoding lecithinase is typical not only for *L. monocytogenes*, but also for *L. seeligeri* and *L. ivanovii*, but not for *L. innocua* [82]. At the same time, *L. monocytogenes* is characterised by induction of lecithinase activity when activated charcoal is added to the nutrient medium, whereas *L. ivanovii* is characterised by lecithinase activity irrespective of the presence of activated charcoal in the incubation medium, and *L. seeligeri* is characterised by the absence of lecithinase activity irrespective of the presence of activated charcoal in the incubation medium [21], which is most likely due to interspecific differences in the regulation of the expression of pathogenicity factors. One of the reasons for the increased production of lecithinase and other pathogenicity factors in *L. monocytogenes* is the activation of the positive regulator of pathogenicity factor expression PrfA [137], which is highly homologous in *L. monocytogenes*, *L. ivanovii*, and *L. seeligeri*, but differs by 3 amino acid residues in these species, possibly affecting its functionality.

The increase in the production of pathogenicity factors (particularly lecithinase) by *L. monocytogenes* in the presence of activated charcoal is associated

with its adsorption and, consequently, the elimination of the autorepressor product produced by *Listeria* itself from the incubation medium [75]. In this connection, the restoration of *Listeria*'s ability to produce lecithinase upon addition of the sorbent to the incubation medium should not depend on the composition of the cultivation medium. At the same time, in the studies of some specialists a significant difference in the induction of lecithinase activity on different media, including media of the same name, produced by different manufacturers, was found, which may be due to the following reasons. Firstly, the components of the medium can influence the adsorption capacity of carbon, in particular, even trace amounts of detergents can reduce the adsorption properties of carbon. Secondly, the increase in lecithinase activity when a sorbent is added to *Listeria* incubation medium may be due not only to an increase in the amount of lecithinase produced, but also to an increase in its lecithinase activity depending on the influence of external factors, the concentration of which in the medium may vary.

Differentiation of species of the genus *Listeria* based on motility at certain temperatures is complicated by the fact that some strains of *L. innocua* showed motility at both 37°C and 20°C, while some strains of *L. welshimeri* remained immobile at room temperature [21].

Another biochemical feature of bacteria of the genus *Listeria* is the ability to hydrolyse 4 carbohydrates (manitol, rhamnose, raffinose and D-xylose), but this ability cannot be used to differentiate *L. monocytogenes* from *L. innocua* [21].

Other methods of bacteriological identification of *Listeria*, which allow differentiating pathogenic and non-pathogenic species, often give contradictory results. In particular, the β-haemolysis characteristic of *L. monocytogenes* on blood agar is weakly expressed in some strains, and some strains show no haemolytic activity at all [21].

To date, bacteriological confirmation of listeriosis is the only reliable way to make a final diagnosis [42], which necessitates the development of new approaches for isolating, typing, and identifying virulent strains of *Listeria* in order to identify the most significant of them in human infectious pathology.

At the same time, the duration of investigations by bacteriological methods varies from 3–4 days for negative results to 10–11 days to confirm a positive result. In addition, the detection of *L. monocytogenes* in animal products by microbiological methods is often difficult due to the high concentration of competitive microflora, the presence of *Listeria*-inhibiting food components and the generally low level of *L. monocytogenes* in samples [122]. Finally, the bacteriological characterisation of *Listeria* in clinical samples is sometimes difficult due to the variability of *Listeria* and its tendency to form coccoid forms [21], predisposing cases of false identification of *Philococcus, Corynebacterium* and *Enterococcus* as *L. monocytogenes* and vice versa. At the same time, the parallel use of biochemical methods, and, in particular, the typical for *L. monocytogenes* induction of lecithinase activity in the incubation medium in the presence of sorbents makes it possible to reliably identify *L. monocytogenes* from lecithinase-producing *Enterococcus* spp. and *Escherichia coli*, whereas the absence of lecithinase activity in the medium without sorbents distinguishes *L. monocytogenes* from staphylococci.

Although serological methods are adjunctive in the diagnosis of listeriosis, they are often effective and provide relatively rapid results, ease of reaction, and the ability to test a variety of biomaterial.

Serological reactions used for the diagnosis of listeriosis include enzyme-linked immunosorbent assay (ELISA), agglutination reaction (RA), complement binding reaction (CBR), indirect haemagglutination reaction (IHGR), and indirect immunofluorescence reaction (NIRF). Blood and cerebrospinal fluid can be used as test material, and the result is considered positive when the antibody titre is from 1:250 to 1:5000 [32].

In the laboratory diagnosis of listeriosis, two serological methods are most often used: complement binding reaction with inactivated cytoplasmic antigen and indirect haemagglutination reaction with erythrocyte antigenic diagnosticum [2], which are not highly specific. In general, serological diagnosis of listeriosis is not sufficiently effective due to false-positive results, the diverse antigenic structure of the bacterium, the antigenic affinity of *Listeria* with other microorganism species, and the technical conditions of the reactions [34].

Most serological methods for the detection of *Listeria* are based on the use of monoclonal antibodies, which was the first method for typing *L. monocytogenes* serotypes [72]. However, this method is time-consuming and has a low differential capacity [98]. Therefore, molecular typing methods have become increasingly popular for *Listeria* typing [72], including ribotyping, multi-target enzyme electrophoresis (MLEE), pulsed-field gel electrophoresis (PFGE), and multi-target sequencing (MLST) [90]. Meanwhile, PFGE is considered the gold standard method for determining *Listeria* subtypes because of its differential ability, reproducibility and repeatability [109].

The first monoclonal antibodies for the detection of *Listeria* showed specificity to a common flagellar H-antigen typical for *L. monocytogenes*, *L. ivanovi*, *L. innocua*, *L. weishimeri* and *L. seeligeri*, but not for 30 cultures of other species, including staphylococci and streptococci [80]. Subsequently, a genus-specific panel of monoclonal antibodies developed by B.T. Butman et al. [53], including 15 specific antibodies showing affinity to thermostable rhodospecific protein with molecular mass from 30 000 to 38 000 Da and not cross-reacting with 21 species of other microorganisms, including streptococci. Two monoclonals from this panel were subsequently used to create a commercial immunoenzyme test

system (*Listeria* — EEK) for the detection of *Listeria* spp. [62], which has found widespread use as an additional, but not alternative, method for the detection of *Listeria* spp. in food [138].

At the same time, polyclonal antibodies used in the immunofluorescence method and monoclonal antibodies are currently not practically used for the diagnosis of listeriosis and retain practical significance only in livestock facilities for the prevention of listeriosis in animals and service personnel [39].

Currently, serological methods used in clinical laboratory diagnostics and aimed at detecting specific antibodies to *Listeria* have been developed. One of the relatively specific serological methods is the detection of antibodies to listeriolysin O, the terminal polypeptide fragment of the recombinant molecule of which is the most specific when screening sera of listeriosis patients compared to other protein antigens [84]. At the same time, experts recommend using this serological method only to detect non-invasive asymptomatic forms of the disease in epidemic outbreaks of listeriosis [53]. When analysing the sera of donors and patients with listeriosis, it is advisable to detect antibodies to the protein antigens of *Listeria (irpA, InlB* and *actA)* associated with pathogenicity [24, 84]. Specific antibodies to *Listeria* antigens are detected in the blood from the second week of the disease and persist for several years after recovery.

At the same time, it is known that *Listeria* serovars and serotypes are not speciospecific and may be common to different *Listeria* species regardless of their pathogenicity for humans. In particular, *L. monocytogenes* is characterised by one or more common antigenic determinants with *Listeria* species other than *L. welshimeri.* In this regard, serovar identification alone, without the use of other methods, does not accurately identify listeriosis [50].

Thus, serological methods for diagnosing listeriosis have a number of disadvantages, including low specificity (*Listeria* antigens are very similar in structure to antigens of other microorganisms, so false-positive or false-negative results are often obtained), the possibility of detecting not the pathogen itself, but only antibodies to it, low reliability of the results, false-negative reactions in severe immunodeficiency states even in very severe course of listeriosis, and the possibility of performing the analysis of *Listeria* antigens. In general, the results of serological tests provide certain information about a patient's possible contact with the pathogen, but do not allow diagnosing listeriosis with a high degree of accuracy even when several serological methods are used, including due to the antigenic affinity of *Listeria* with staphylococci, enterococci and erysipeloid [20].

The diagnosis of listeriosis can be suspected or made if there is a reliable difference in antibody titres in paired sera of patients with a characteristic clinical picture (RA with coloured diagnostics, RBC, NIRF, RNAS), cerebrospinal fluid (NIRF, PCR, ELISA, microscopy) and bacteriological examination by enrichment with charcoal immunoglobulin sorbent [13, 39, 42].

At the same time, serological methods of laboratory diagnostics of listeriosis remain the main methods in the practice of Russian bacteriologists and allow establishing the presumed diagnosis with further confirmation by bacteriological methods [40]. However, the slide agglutination method is relatively simple and reliable, requiring the availability of agglutinating listeriosis sera, the improvement of methods for obtaining which is very important at present.

One of the relatively fast, highly effective methods for the detection of *L. monocytogenes* is the molecular biological method of PCR and enzyme immunoassay [27] using the highly specific chromogenic medium ALOA-agar [48].

The specificity and high sensitivity of PCR have been confirmed on various strains of pathogenic *Listeria*, but poor lysis of some *Listeria* strains, apparently related to the structure of the cell wall, may give false-negative results [21]. In this regard, some specialists recommend PCR using *Listeria* cells added to the reaction mixture without pretreatment with lytic enzymes [67]. In addition, the multi-targeted variable number of tandem repeats assay (MLVA), a PCR-based typing method that characterises bacteria by detecting tandem repeats at several specific loci in the bacterial genome, is quite informative [79, 108].

Matrix Assisted Laser Desorption/Ionisation Time of Flight (MALDI-ToF) is a relatively effective method for the identification of *L. monocytogenes* [12]. At the same time, there are reports in the literature that species identification of *Listeria* species by MALDI-ToF is not always correct, which may be due to the influence of various factors, such as cultivation conditions, the composition of nutrient media, and the level of polymorphism of strains taken for research [89, 125].

Real-time polymerase chain reaction is a comparatively fast and practical alternative to the microbiological method for the detection of *Listeria* [35]. Therefore, the development of species-specific PCR methods for the detection of the *L. monocytogenes* genome is an urgent task. For PCR identification of *L. monocytogenes*, various genes are used as targets: 16S and 23S rRNA, *prs, gyrB, rpoB, hly, inlA* and *inlB, plcA, iap*, etc. [17, 21, 69, 113, 121, 147]. At the same time, the real-time PCR method does not allow distinguishing viable bacterial cells from non-viable ones; therefore, positive results obtained using this method must necessarily be confirmed by a traditional microbiological method [35].

To determine the serological affiliation of *Listeria* cultures, according to the world classification, it is recommended to use the multiplex PCR method based on the correlation between the serogroup affiliation of an isolate and the presence of specific open reading frames in its genome [9, 16], which makes it possible to identify the diversity of *L. mono-*

cytogenes cultures and differentiate the strains of epidemic significance and danger to humans [39].

To obtain *Listeria* isolation media, it is necessary to study the optimal conditions for their growth and reproduction and to determine the optimal concentrations of nutrient elements. *Listeria* have been found to grow on simple nutrient media, capable of reproduction in a wide range of temperatures (4–45°C), pH (5.0–9.0), and humidity, in the presence of 20% NaCl and 15% CO_2 [29, 49]. The high metabolic plasticity of *Listeria* determines the possibility of their transition from the saprophytic phase to the parasitic phase and vice versa; optimal cultivation conditions are necessary to preserve the virulent properties of *Listeria*, which is important for the accumulation of full biomass [29]. At the same time, the cultivation conditions (composition of nutrient media, temperature and incubation time) influence the polymorphism of *Listeria*, which complicates the estimation of the results of bacteriological analysis and may lead to errors in diagnosis [5]. In particular, the prolonged stay of *Listeria* in cold storage predetermines the presence of most of the microorganisms at the L-transformation stage, which requires a long time of their reversion in enrichment media for the detection of pathogens [5]. In this regard, accurate diagnosis of *Listeria* requires the use of methods such as DNA diagnosis, PCR and ELISA [5].

At the same time, accelerated methods such as ELISA, PCR, DNA-DNA and DNA-RNA hybridisation, radioimmunological methods, and the use of chromogenic nutrient media are the most suitable for the detection of *L. monocytogenes* in perishable products, which are characterised by high speed of analysis, sensitivity and specificity, and low consumption of nutrient media. High sensitivity and specificity in detecting *L. monocytogenes* has been shown for the test system LOCATE® *Listeria*, in which highly specific monoclonal antibodies to thermostable O-antigens or somatic antigens of the *Listeria* cell wall are used as antibodies [6]. Proteomics methods involving mass spectrometric analysis of proteins are also used to diagnose listeriosis [31].

Conclusion

Throughout their long evolution, pathogenic *Listeria* have developed a set of unique mechanisms that allow them, along with a saprophytic lifestyle, to switch to intracellular parasitisation, avoiding contact with the humoral immune system and suppressing at the initial stages of infection the Th1-type immune response, which is essential for the elimination of intracellular parasites. In addition, *L. monocytogenes* is able to switch on phagocytosis in those cells for which it is not usually characteristic, which predetermines the possibility of its invasion of a wide range of target cells and significantly complicates the course of listeriosis.

Ecological plasticity and tolerance of *Listeria* determine their ability to change from saprophytic to parasitic way of life and to reverse back to saprophyticism when they enter the environment and survive under different environmental conditions. At the same time, non-pathogenic *Listeria*, as well as pathogenic microorganisms forming a biocenosis with *L. monocytogenes*, can serve as a reservoir of pathogenicity and resistance determinants and be transmitted to pathogenic *Listeria* by horizontal transfer. Thus, the high degree of genetic relatedness of *L. monocytogenes* with *L. innocua* makes it possible for *L. innocua* to create reservoirs of resistance genes that can be transferred to *L. monocytogenes*, including virulence genes. In addition, pathogenicity genes can be transferred from *L. monocytogenes* to *L. innocua*, which predetermines the emergence of atypical haemolytic pathogenic strains, which, given the greater prevalence of *L. innocua* in the environment, may pose a greater threat to humans and animals.

The constant evolution of pathogenic *Listeria* and their acquisition of new surface antigens, in turn, complicate the laboratory diagnosis of listeriosis and differential typing of *Listeria* in the food industry and require the development of new immunobiological preparations, culture media and modern schemes for the isolation and identification of *L. monocytogenes*.

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