Lactobacillus Genus Complex

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Microorganisms belonging to the *Lactobacillus* genus complex (LGC) are naturally associated or deliberately added to fermented food products and are widely used as probiotic food supplements. Moreover, these bacteria normally colonize the mouth, gastrointestinal (GI) tract, and female genitourinary tract of humans. They exert multiple beneficial effects and are regarded as safe microorganisms. However, infections caused by lactobacilli, mainly endocarditis, bacteremia, and pleuropneumonia, occasionally occur.

Keywords: Lactobacillus species ; opportunistic pathogens

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1. Introduction

Bacteria currently classified in the genus *Lactobacillus* are a paraphyletic group of gram-positive, non-spore forming, mostly non-respiratory, but aerotolerant, lactic acid bacteria (LAB), comprising at this time more than 237 species and 29 subspecies (http://www.bacterio.net/lactobacillus.html) [1]. Morphologically, they can be elongated or short non-motile rods, frequently found in chains and sometimes bent. They produce lactic acid as a major end-product of carbohydrate fermentation.

Lactobacilli are part of the normal human microbiota that colonizes the mouth, gastrointestinal (GI) tract, and female genitourinary tract. Moreover, these bacteria have been used for centuries for food and feed fermentation processes aimed at the transformation of perishable raw materials of animal or plant origin into more preservable products. Their activities are relevant to the production of dairy products, bread, sausages, fermented vegetables, wine, and silage.

According to the type of sugar fermentation pathway, lactobacilli fall into the following three groups, all including species that are industrially exploited: (i) obligately homofermentative, that produce only lactic acid as an end product of carbohydrate metabolism through the glycolysis pathway; (ii) facultatively heterofermentative, that produce a mixture of lactic and acetic acid as end products of carbohydrate metabolism through the glycolysis or the phosphoketolase pathway, and; (iii) obligately heterofermentative, that produce lactic and acetic acid, or ethanol, and CO_2 as end products of carbohydrate metabolism through the phosphoketolase pathway [2].

The genome size of *Lactobacillus* spp. is highly variable, ranging between about 1 and more than 4 Mb. Genome size also varies within a single species [3] as a result of genome decay in strains adapted to specialized niches where genes encoding for multiple substrate utilization are lost [4].

Based on whole genome phylogeny, genera *Fructobacillus*, *Leuconostoc*, *Oenococcus*, *Pediococcus*, and *Weissella* were found to descend from the most recent common ancestor of *Lactobacillus*, so that they constitute internal branches of the *Lactobacillus* taxon for which the designation "*Lactobacillus* genus complex" (LGC) has been proposed [5]. For this reason, members of the LGC not classified as *Lactobacillus* spp. were also considered in this entry.

Zheng et al. (2015) [3] found a good correspondence between metabolic groups and phylogenomics based on 172 concatenated protein sequences encoded by single copy genes of core genomes and key enzymes of metabolic pathways.

LGC organisms better characterized physiologically and technologically are those of highest relevance for natural or industrial food fermentation, probiotic properties, and biotechnological applications. In **Table 1**, those most frequently used in food technology and as probiotics are listed, together with type of metabolism, main ecological niche, and technological applications.

Table 1. *Lactobacillus* species most frequently used in food technology and as probiotics, type of metabolism, technological applications, and typical ecological niches.

Species	Metabolism	Main Ecological Niches	Main Technological Applications
L. acidophilus	**homofermentative**	**GIT, dairy products [6]**	**Probiotic [6]**
L. brevis	**heterofermentative**	**Fermented vegetables, GIT [7]**	**Sourdough fermentation [8]**
L. buchneri	**heterofermentative**	**Fermented vegetables, dairy products, GIT [9]**	**Silage fermentation [10]**
L. casei/paracasei	**facultatively heterofermentative**	**Dairy products, GIT [11]**	**Cheese production, probiotic [12]**
L. delbrueckii* subsp. *bulgaricus* and *lactis	**homofermentative**	**Dairy products [13]**	**Fermented milk and cheese production [13]**
L. helveticus	**homofermentative**	**Dairy products [4]**	**Cheese production [4]**
L. plantarum	**facultatively heterofermentative**	**Fermented food and feed, GIT [14]**	**Cheese, sausage, fermentation of vegetables, silage production, probiotic [14]**
L. reuteri	**heterofermentative**	**GIT, skin and mucosae [15]**	**Probiotic [15]**
L. rhamnosus	**facultatively heterofermentative**	**Dairy products, GIT [11]**	**Probiotic [16]**
L. sakei	**facultatively heterofermentative**	**Meat, vegetables [17][18]**	**Sausage fermentation [18]**
L. sanfranciscensis	**heterofermentative**	**Sourdough [19]**	**Sourdough fermentation [19]**
L. salivarius	**homofermentative**	**Human and animal GIT [20]**	**Probiotic [20]**
Oenococcus oeni	**heterofermentative**	**Grape berries [21]**	**Wine malolactic fermentation [21]**
Pediococcus acidilactici	**homofermentative**	**Plant materials, cheese, fermented meat products, GIT [22]**	**Sausage fermentation, probiotic [22]**
P. pentosaceus	**homofermentative**	**Plant materials, cheese, fermented meat products, GIT [22][23]**	**Sausage fermentation, probiotic [22]**

GIT: gastrointestinal tract.

Culture-independent DNA-sequence analysis put in evidence that autochthonous *Lactobacillus* organisms represent, at most, 1% of the total bacterial population in the distal human gut. Their number changes in some diseases, such as Crohn’s disease, human immunodeficiency virus (HIV) infection, rheumatoid arthritis, multiple sclerosis, obesity, type 1 and 2 diabetes, irritable bowel syndrome, and prenatal stress. However, the role of autochthonous intestinal lactobacilli in disease prevention and treatment must be still elucidated [24].

A metagenomic analysis on a human subject showed that over a period of two years, more than 50 *Lactobacillus* species, and individual *Lactobacillus* genotypes, were repeatedly detected in numbers of up to 10^8 cells/g in the stool [25], suggesting that a persistent population of lactobacilli could inhabit the gastrointestinal tract (GIT) of individuals.

Lactobacillus species inhabiting human GIT and isolated from faeces comprise most of the microorganisms listed in **Table 1** [23][26]. The species *L. antri*, *L. gastricus*, *L. kalixensis*, *L. reuteri*, and *L. ultunensis* have been isolated from the stomach mucosa [27]. Lactobacilli also occur naturally in the human mouth [28]. Another site colonized by lactobacilli is the vagina, where *L. crispatus*, *L. gasseri*, *L. jensenii*, *L. vaginalis*, and *L. iners* are commonly found [29].

The efficacy of lactobacilli as probiotics derives from their ability to tolerate very low pH values, which allows them to survive transit through the stomach, and adhere to the mucus layer by surface structures, such as pili and cell-wall anchored proteins [30]. Some of their beneficial activities are favoring GIT health by inhibiting the growth of pathogenic organisms with the production of lactic acid and other metabolites. Some *Lactobacillus* strains are able to immunomodulate human cells and elicit an anti-inflammatory response [31]. In addition, some strains produce antioxidants [32].

As other probiotics, they are sold as constituents of food, food additives, or food supplements, but control on their use to safeguard consumer’s health needs to be improved [33].

Lactobacillus organisms are rarely associated with pathology in immunocompetent people, but in the presence of risk factors and underlying conditions, they can cause infections such as endocarditis, bacteremia, neonatal meningitis, dental caries, and intra-abdominal abscesses including liver abscess, pancreatic necrosis infection, pulmonary infections, pyelonephritis, meningitis, postpartum endometritis, and chorioamnionitis [34][35].

2. Members of LGC as Opportunistic Pathogens

The risk factors most commonly reported for *Lactobacillus* infections are diabetes mellitus, pre-existing structural heart disease (in infective endocarditis cases), cancer (especially leukemia), total parenteral nutrition, broad spectrum antibiotic therapy [36][37], chronic kidney disease, inflammatory bowel disease, pancreatitis [38], chemotherapy, neutropenia, organ transplantation (especially liver transplantation) [39], HIV infection [40], and steroid use [41].

Moreover, perinatal infections caused by lactobacilli indicate preterm neonates as a population category at risk. Though a meta-analysis indicated that probiotics reduce the incidence of necrotising enterocolitis and all-cause mortality in preterm infants, excluding infants with a birth weight of <1000 g, cases of infections in premature infants have been reported. These include late-onset sepsis due to *L. rhamnosus* following a laparotomy, amnionitis, and neonatal meningitis, cases of bacteremia, lactobacillemia of amniotic fluid origin, *L. rhamnosus* GG bacteremia associated with probiotic use in a child with short gut syndrome, and *L. rhamnosus* infection in a child following bone marrow transplantation [42][43][44].

Experiments with athymic mice have shown the potential for probiotics to cause sepsis in immune deficient neonates. This possibility was supported by case reports of probiotic sepsis in humans [45].

The most common predisposing events for *Lactobacillus* infections are dental manipulation, poor dental hygiene, intravenous drug abuse, abdominal surgery, colonoscopy, probiotic use, and heavy dairy product consumption [46].

Recent opinion articles invite safety assessments to be conducted for *Lactobacillus* probiotics, since they represent a risk for individuals with underlying medical conditions [33][47]. In particular, Cohen (2019) [33] stated that the ability of these strains to infect humans is not controversial and that live bacteria sold as commercial probiotics are capable of infecting immunocompromised hosts and have well-established “inherent infective qualities”.

Theoretically, the potential pathogenicity of probiotics may be enhanced in strains selected on the basis of the capacity to adhere to the intestinal mucosa, a trait that is considered important for their mechanism of action. Indeed, adherence can favor translocation across the intestinal barrier and ability to cause infections. The finding that *Lactobacillus* spp. isolated from blood adhere to intestinal mucus in greater numbers than isolates from human feces or dairy products supports the relationship between mucosal adhesion and pathogenicity [34].

2.1. Infections Caused by Members of the LGC

2.1.1. Endocarditis

Among infections caused by lactobacilli, endocarditis, with or without bacteremia, is the most common. It occurred in patients who had dental extractions or gingival bleeding after toothbrushing [48][49], suggesting that these could be considered risk factors, especially in the presence of underlying immunosuppression and valvular heart disease [50].

An *L. rhamnosus* endocarditis case was reported in an 80 year old man who frequently consumed yogurt containing the organism following an upper endoscopy. This patient required aortic and mitral valve replacement for a cure. Cases of *Lactobacillus* endocarditis have also been described following colonoscopy [51]. Patients with hereditary hemorrhagic telangiectasia (HHT) are also exposed to this infection because of telangiectasias and arteriovenous malformations (AVMs). In a habitual consumer of fermented dairy products with this pathological condition, the portal of entry was intestine following a colonoscopy [52].

In a middle-aged man, *L. acidophilus* endocarditis led to an aneurysmal rupture of the sinus of Valsalva into the right ventricular outflow tract with fistula formation from the right coronary sinus to the right ventricular outflow tract that required surgical repair with an aortic valve replacement [53]. A case of mitral valve endocarditis due to *Lactobacillus* was recently reported in an 81 year old woman [54].

P. pentosaceus caused endocarditis in a 66 year old male in association with *Lactococcus lactis* subsp. *lactis* [55].

The species *L. rhamnosus* and *L. casei* have been most frequently involved in endocarditis, presumably for their ability to induce platelet aggregation and generate fibrin by producing a factor Xa-like enzyme that catalyzes steps of the coagulation process favoring clot formation. It is supposed that these bacteria colonize thrombotic vegetations where they grow, evading host defenses [56].

2.1.2. Bacteremia

Lactobacillus bacteremia has been associated with the consumption of probiotics in special medical conditions, including hematopoietic stem cell transplantation [57] and HIV-infection [58].

Bacteremia caused by *Veillonella* and *Lactobacillus* spp., secondary to occult dentoalveolar abscess, was reported in a pediatric patient [59].

In a patient with chronic lymphocytic leukemia and recurrent bacteremia caused by *L. casei/paracasei* and *L. rhamnosus*, the source of infection was unknown, since probiotics had not been assumed and entry from dental infections or the gastrointestinal and urinary tract was excluded [60].

Bacteremia caused by isolates indistinguishable from the *L. rhamnosus* probiotic strain GG based on pulsed field gel electrophoresis (PFGE) typing was associated with a higher mortality rate than bacteremia caused by other *Lactobacillus* species [37].

Lactobacillus sepsis was normally resolved with antimicrobial therapy, but in some cases, patients developed septic shock. In other cases, the outcome has been fatal, but due mostly to underlying diseases rather than probiotic sepsis. On the basis of the characteristics of the cases reported, a list of major and minor risk factors for probiotic sepsis was proposed and caution in using probiotics in the presence of a single major risk factor or more than one minor risk factor was suggested. Major risk factors are being immune-compromised and preterm births, while minor risk factors are presence of central venous catheters (CVCs), impaired intestinal epithelial barrier caused by intestinal infections or inflammation, administration of probiotic by jejunostomy, concomitant administration of antibiotics to which the probiotic is resistant, probiotics with properties of high mucosal adhesion or known pathogenicity, and cardiac valvular disease (*Lactobacillus* probiotics only) [34].

2.1.3. Pleuropneumonia

Lactobacillus species were a primary cause of pleuropneumonia without bacteremia, especially in immunocompromised patients. From 1982 to 2016, 15 cases of pleuropneumonia caused by *Lactobacillus* spp. were reported, and involved *L. rhamnosus*, *L. fermentum*, *L. acidophilus*, *L. paracasei*, and *L. coryneformis*. All the patients had severe associated co-morbidities comprising immunosuppression, caused in most cases by AIDS, carcinoma, chronic diseases, and neutropenia. One patient had *Lactobacillus* pneumonia linked to consumption of a probiotic supplement. The route of entry was probably GIT in some patients, the transplanted lung in one patient, ventilator in an immunocompetent patient with thoracic trauma. In one patient, diagnosed with trachea-esophageal fistula, the route of *Lactobacillus* pneumonia was aspiration of a probiotic strain. Only one patient had concurrent lactobacillemia. The authors of the study suspected that infections due to *Lactobacillus* species are under-reported because appropriate growth conditions, such as microaerophily or anaerobiosis, are not applied in clinical microbiology laboratories for their isolation [61].

2.1.4. Meningitis

The first reported case of meningitis in which *Lactobacillus* was isolated from blood and cerebrospinal fluid was in an early-term neonate (38 weeks gestation) within the first day of life. Transmission from the mother’s genital tract to the neonate’s oral mucosa at the time of delivery was identified as the probable route of infection, since no immunological abnormalities, structural defects, or peripartum complications were observed. Another case involved a 10 year old neutropenic child affected by acute leukemia with four successive episodes of *L. rhamnosus* bacteriemia and unknown origin of infection.

A lethal case of meningitis due to *L. rhamnosus* was reported in an 80 year old woman not immunocompromised but with a fistula between the esophagus and the meningeal space, caused by dislodged and eroded plates and screws used several years earlier for cervical spine surgery, that facilitated bacterial translocation.

Meningoencephalitis caused by *L. plantarum* was reported in a 63 year old man with metastatic planoepithelial lung cancer.

Bacteremia and endocarditis, which are the two main manifestations of *Lactobacillus* infection, can lead to the onset of neurological sequelae through mechanisms mediated by embolic material.

This was not the case of the latter patient, who had no signs of endocarditis. Therefore, direct bacterial dissemination from the gastrointestinal tract was hypothesized [62].

2.1.5. Urinary Tract Infections

Cases of urinary tract infections caused by lactobacilli in women have been reported, with symptoms such as chronic pyuria and pyelonephritis with bacteremia, in which *L. delbrueckii* or *L. jensenii* were the causative microorganisms [63][64][65]. A case of urinary tract infection caused by *Lactobacillus* spp. was reported in a newborn [66].

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