Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/5javwy79

INTESTINAL MICROBIAL COLONIZATION RESISTANCE: A NOVEL DEVELOPMENT IMPACTING GROUP B STREPTOCOCCUS COLONIZATION

Noorulain Hyder[1*], Farzana Sadaf [1], Ale Zehra[2]

[1*]Department of Pharmacology, Faculty of Pharmacy, Hamdard University, Karachi, Pakistan
[2]Department of Pharmacy Practice, Dow College of Pharmacy, Dow University of Health Sciences

***Corresponding Author:** Noorulain Hyder
*Email: Dr.noorulain@hamdard.edu.pk

Abstract:
Premature delivery, suppurative meningitis, pneumonia in neonates, septicemia, intrauterine infections in pregnant women, and even mortality may all be caused by Group B *Streptococcus* (GBS). The U.S. Centers for Disease Control and Prevention advise that all individuals who are pregnant undergo screening for GBS between 35 and 37 weeks of gestation, and those who receive a positive test result should be administered intrauterine antibiotic prophylaxis (IAP). Antibiotics may lead to adverse reactions and are ineffective in preventing GBS, a condition that manifests later in life. Given the rising challenge of antibiotic resistance among bacteria, it is crucial to investigate more efficient and economically viable strategies to prevent infections caused by GBS colonization. GBS is a zoonotic disease that may be spread by food, hence research on its colonization in the intestinal tract is crucial. Intestinal symbiotic bacteria may lower the chance of GBS retrogradely infecting the reproductive system by preventing intestinal pathogens from colonizing and growing via an intestinal colonization resistance mechanism. This approach holds significant promise as a leading strategy for preventing GBS. This article focused on the effects of probiotics derived from intestinal colonization resistance on GBS colonization infection.

Key Words: Probiotics, intestinal colonization resistance, GBS, and antibiotic resistance

In the 1930s, Group B Streptococcus (GBS) was isolated from cows with mastitis by Rebecca Lancefield and was also named Streptococcus agalactiae. It is a facultative anaerobic Gram-positive coccus [1]. Vertical transmission is the main route of GBS transmission, while GBS can also be transmitted through food.As a zoonotic pathogen, it has been reported to cause foodborne invasive infections in many parts of Southeast Asia [2-6]. GBS can intermittently, transiently, or persistently colonize the human digestive and reproductive tracts, with a carrier rate of 15% to 35% in healthy individuals [7]. At the same time, GBS is a conditionally pathogenic bacterium with multiple virulence factors. When the host's immune response weakens or under specific environmental conditions, these virulence factors are activated to work together in the host's body, aiding in adhesion and colonization, triggering inflammation, and interfering with host cell signaling, thereby progressing from a colonization state to causing invasive diseases [8].According to capsular antigenicity, GBS is divided into 10 serotypes: Ia, Ib, and II to IX [1,9].Although there are certain differences in the distribution of serotypes across countries worldwide, the main serotypes causing GBS disease are primarily types III, Ia, Ib, II, and V, which can cause invasive diseases in more than

90% of infants and young children[10]. It is very common for women of childbearing age to carry GBS in their vagina, intestines, and urinary tract.Research indicates that the colonization rate of GBS in the reproductive tract of pregnant women in China is around 20%, whereas in European and American countries, this colonization rate is as high as 40% to 50%[11].The guidelines from the Centers for Disease Control and Prevention recommend collecting vaginal and rectal specimens from pregnant women at 35-37 weeks of gestation for GBS screening [10,12-13].The physiological structure of females makes the rectum and the urogenital tract relatively close to each other. There is currently evidence indicating gut-vaginal microbiome cross-talk [13]. The colonization of GBS in the intestines of adults, especially women of childbearing age, should be given high attention [14]. The gut microbiome is a dynamic and diverse ecosystem composed of trillions of microorganisms, performing various activities such as metabolic regulation, nutrient digestion, and immune response modulation [15]. The gut microbiota has the ability to inhibit the colonization and expansion of intestinal pathogens, a characteristic known as colonization resistance. This is an important function of a healthy microbiota [16]. The mechanisms of colonization resistance are not yet fully understood. Generally speaking, the gut microbiota enhances colonization resistance against intestinal pathogens through both direct and indirect mechanisms. The former, known as microbiota-specific colonization resistance mechanisms, refers to the ability of the microbiota to promote direct colonization resistance by competing for resources within the gut and producing inhibitory compounds. The indirect mechanism involves symbiotic bacteria indirectly controlling invading pathogens by regulating the gut barrier and enhancing the host's innate immunity in the gut [17]. This article focuses on the resistance to intestinal colonization and its impact on GBS colonization. The influence of the dye and the utilization of probiotics derived from it.

1Detriment of GBS

1.1. Impact of GBS on Pregnant Women

Under typical conditions, GBS engages in competition and limitation with other microorganisms in the reproductive tract and does not lead to disease. During pregnancy, elevated estrogen levels in pregnant women may lead to certain conditionally pathogenic bacteria becoming active pathogens, thereby disrupting the vaginal microecological balance.

Research indicates that factors including age of 35 years or older, a history of miscarriage, gestational diabetes, vaginal cleanliness grade III or IV, and CRP levels of 60 mg/L or higher are associated with an increased risk of GBS colonization in women during late pregnancy. The impact of these factors can result in different levels of harm to the vaginal microenvironment. Current evidence suggests that the interaction between the gut and vaginal microbiomes, coupled with diminished resistance of the urogenital tract to pathogens, may elevate the risk of retrograde GBS infection [14]. The decline in immune function and the imbalance of the vaginal microenvironment in women during late pregnancy can lead to the ascent of pathogenic bacteria, resulting in infection of the pregnant uterus and membranes. The proteinase generated by GBS has the capacity to directly invade the membranes, causing premature rupture; additionally, GBS can induce substantial uterine contractions, which may lead to preterm birth.Moreover, GBS has the potential to persistently ascend and infect the uterus, resulting in heightened uterine tension and an elevated risk of postpartum hemorrhage, thereby posing significant risks to the lives of both mothers and infants.In conclusion, GBS infection is associated with several negative pregnancy outcomes, including preterm birth, postpartum hemorrhage, premature rupture of membranes, intrauterine infection, and puerperal infection. It is crucial to highlight the management of GBS infection in perinatal women, focusing on early screening and preventive strategies to mitigate the risk of GBS infection in this population and its effects on newborns [18-19].

1.2 The Impact of GBS on Newborns

Severe neonatal infections resulting from GBS have attracted significant social attention. The majority of GBS infections are passed from mother to child, exhibiting a vertical transmission rate of 45.2% during vaginal delivery and 25.9% during cesarean section [20].Neonatal GBS disease is

categorized by the timing of its onset: early-onset GBS disease (GBSEOD) is the more prevalent form, manifesting within the first 7 days post-birth, primarily influenced by maternal colonization of the genital and gastrointestinal tracts by GBS, which serves as the principal risk factor.The majority of cases of GBS-EOD arise from the colonization of GBS in the mother's vagina, which can be transmitted to the newborn via ascending infection, aspiration of amniotic fluid during delivery, placental transmission, or passage through the birth canal. About half of pregnant women who are colonized with GBS will pass the bacteria on to their infants. Given the low immunity of newborns, 1% to 2% may develop GBS-EOD, which can result in serious conditions such as purulent meningitis, sepsis, or pneumonia. Once early-onset GBS-EOD manifests, Infection, with neonatal mortality rates as high as 50%, is a significant cause of morbidity and mortality in the first week after birth [21-22]. Late-onset GBS disease (GBSLOD) usually occurs in newborns infected with GBS from breast milk or the environment, occurring between 7 days and 3 months after birth [23]. GBS can invade the brain epithelium after colonizing the neonatal bloodstream through the digestive tract, with the main clinical manifestation being sepsis, and 40% of the affected infants also having meningitis. However, the progression of GBS-LOD is rapid, with the possibility of sudden outbreaks, developing into toxic shock and convulsions within hours, with a very high mortality rate. Currently, there is no suitable method to prevent GBS-LOD [9]. GBS remains one of the important pathogens for bacterial infections in newborns and is also a major cause of death from neonatal pneumonia.

2. Antibiotic prevention, treatment, and resistance of GBS

Since the 1970s, Western countries have placed great emphasis on the prevention and treatment of GBS in pregnant women during the perinatal period. GBS, as an opportunistic pathogen, does not require treatment when colonizing the reproductive or intestinal tract of non-pregnant adults. However, for pregnant women who test positive for GBS screening in late pregnancy, primary prevention of GBS-EOD through intrapartum antibiotic prophylaxis (IAP) is of great significance. The first choice is intravenous penicillin, followed by intravenous ampicillin.Pregnant women with penicillin allergies, low risk of allergic reactions, or uncertain severity of reactions can use first-generation cephalosporins.For pregnant women at high risk of allergic reactions, clindamycin can only be used as a substitute for penicillin if the GBS susceptibility results show sensitivity to clindamycin.For pregnant women at high risk of penicillin allergy and whose GBS isolates are resistant to clindamycin, intravenous vancomycin may be considered[10]. GBS-LOD is a common cause of neonatal sepsis. The initial empirical treatment when neonatal sepsis is suspected is the use of ampicillin and gentamicin, which have anti-GBS activity. However, the use of these two drugs has side effects such as ototoxicity and nephrotoxicity [24]. Regarding the treatment of neonatal GBS infection, the choice, duration, and safety of antibiotics have always been controversial. Many retrospective studies indicate that prolonged initial empirical antibiotic treatment may easily lead to adverse outcomes in premature infants [25-27]. Even if GBS infection is cured, 25% to 35% of children may still experience permanent neurological damage such as hearing impairment, vision impairment, developmental delays, or cerebral palsy as sequelae [28]. In recent years, the unreasonable use of antibiotics in clinical settings has led to the phenomenon of GBS resistance. For example, GBS resistance to macrolides is severe, with 100% resistance to azithromycin and roxithromycin, and the occurrence of multidrug resistance is becoming increasingly common [29]. Moreover, the use of antibiotics can have side effects on the human body, such as allergic reactions in women [30], obesity and diabetes in pregnant women [31], changes in the gut microbiome of newborns, allergies in newborns, and late-onset infections in preterm infants. Additionally, IAP cannot prevent GBS-LOD in infants aged 7 to 89 days. Therefore, the GBS prevention guidelines in Europe and the United States strictly limit the indications for IAP, focusing on the development of non-antibiotic methods to reduce vertical transmission of GBS [32].

3. Intestinal Colonization Resistance

1.1 Microbiome-Specific Colonization Resistance Mechanisms

The direct mechanisms of colonization resistance are characterized by the symbiotic microbiome,

which, through bacterial factors, restricts the colonization of exogenous pathogens or prevents the excessive growth of pathogenic indigenous microorganisms. Direct mechanisms occur between bacteria, where bacteria directly inhibit the growth of pathogens by competing for resources (exploiting nutrients and living space) or producing inhibitory compounds (such as bacteriocins and short-chain fatty acids), with the host serving as the environment where this competition takes place [33-34]. Nutritional competition is an important determinant of gut community composition and colonization resistance. In the intestinal environment, the microbiota competes with pathogens for nutrients in the gut to sustain itself and its population growth. Particularly, bacterial populations of the same species often require similar nutrients, leading to more intense competition for these resources [35]. There is relatively little research on nutritional competition against GBS; this paper mainly discusses the more abundant and well-studied bacteriocins and fatty acids and their inhibitory effects on GBS growth and colonization.

1.1.1 Bacteriocins

Bacteriocins are short peptide molecules produced by bacteria that have antibacterial or bactericidal activity. They typically kill bacteria by forming pores in the bacterial cell membrane and interfering with RNA and DNA metabolism [36]. Bacteriocins of Gram-positive bacteria are mainly produced by lactic acid bacteria (such as *Lactococcus* and *Lactobacillus*) and some streptococci [37]. Lactic acid bacteria are part of the normal flora in the intestines and vagina. They can not only inhibit the growth of GBS by producing hydrogen peroxide and lactic acid, but some members of the Lactobacillus genus can produce bacteriocins. Bacteriocins can inhibit various Gram-positive bacteria, and they can work synergistically with erythromycin to inhibit the growth of GBS [38]. Research indicates that lactocin and vancomycin target the same site: lipid II, a precursor of the bacterial cell wall. The high-affinity binding of lactocin to lipid II can cause pores to form in the bacterial cell wall and expose the peptidoglycan layer. Nanomolar levels of lactocin can exhibit bactericidal activity against Gram-positive bacteria [39]. Malgorzata's in vitro studies indicate that *Lactobacillus plantarum* C11 can secrete plantaricin E, F, J, and K, and the supernatant from its cultures that remove hydrogen peroxide and lactic acid is effective against major pathogenic bacteria. The Qing-type GBS has a strong inhibitory effect [40]. Ruíz et al. [41] isolated Lactobacillus fermentum and *Lactobacillus rhamnosus* from the vagina and found that the bacteriocin-like inhibitory substances from both exhibited synergistic inhibitory activity against the growth of GBS. In addition to lactocins from *Lactobacillus* species, probiotics such as *Enterococcus* also exhibit antagonistic activity against GBS, with enterocins A and B showing antagonistic activity against GBS [42]. Salivarius K12 produces salivary peptide A and salivary peptide B, which can reduce GBS growth in vitro. Administration of salivarius K12 can decrease the persistence of GBS vaginal colonization in mouse models [43]. Furthermore, some pathogens can also produce bacteriocins that inhibit GBS growth, but due to safety concerns, they cannot be used as probiotics [44] Currently, the drawbacks of antibiotics are evident, and bacteriocins are highly promising antimicrobial agents that deserve further attention and exploration [45].

1.1.2 Fatty Acids

Short-chain fatty acids (SCFAs) are produced by the anaerobic fermentation of dietary fiber and resistant starch by the gut microbiota. Acetate, propionate, and butyrate are the three main SCFAs, accounting for more than 90% of the SCFA pool [46]. *Bifidobacterium*, as a widely used probiotic, can produce abundant SCFAs to inhibit GBS growth [47]. In the colon, butyrate-producing bacteria can utilize dietary fiber and resistant starch to produce abundant butyrate. Studies have shown that pregnant women who orally take butyrate-producing bacteria daily before delivery have a lower rate of GBS positivity in the vagina and rectum [48]. In addition, there is lactic acid in the gut, which is very important for gut health, besides SCFAs. *Lactobacillus* produces a large amount of lactic acid, which has the function of inhibiting the growth and adhesion of GBS. As an acidic substance, it can lower the pH, leading to the accumulation of protons within the bacteria to inhibit pathogens [49]. However, GBS can respond to low pH values through a series of different defense mechanisms, such

as proton pumps and increasing alkaline compounds within the bacteria to induce a buffering effect. Studies have shown that the antibacterial effect of lactic acid is superior to that of hydrochloric acid, and the lactic acid bacteria strains that can produce the highest levels of lactic acid exhibit the strongest antagonistic effect against GBS [50-51]. In summary, the inhibition of GBS by SCFAs is not only through lowering pH; the specific mechanisms still need to be studied.

3.2 Indirect Colonization Resistance Mechanisms

In addition to direct competition and the production of inhibitory compounds, the gut microbiota can also indirectly regulate colonization resistance by enhancing the intestinal mucosal barrier and the immune system. This is characterized by the microbiota's reliance on host-derived factors to provide protection against exogenous pathogens. Probiotics can stimulate the innate immune response, helping the intestinal immune system mature, thereby preventing intestinal diseases [17, 52].

3.2.1 Regulation of the Gut Barrier

The adhesion of Group B *Streptococcus* (GBS) to the surface of intestinal epithelial cells (IEC) is a key process in its invasion of host barriers and pathogenic infection. The main adhesins mediating the interaction between GBS and intestinal epithelial cells include fibrinogen-binding protein, laminin-binding protein, and Group B *Streptococcus* C5a peptidase, which are also its main virulence factors [53-54]. GBS adhesion to intestinal epithelial cells requires breaking through the intestinal mucus layer [55]. The main components of the colonic mucus barrier are mucins (mucoprotein, MUC) secreted by goblet cells, water, inorganic salts, antimicrobial peptides, etc. It is divided into two layers of mucus with different physical properties: the dense layer adhering to the intestinal epithelial cells acts as a barrier, isolating intestinal microorganisms from IECs and immune cells; the looser mucosal layer closer to the intestinal lumen is thicker and serves as a habitat for a large number of intestinal microorganisms. The number of these adhesion sites is fixed, and probiotics can protect the host by competing with pathogens like GBS for these sites [49,56]. Recent studies have shown that probiotics play a key role in regulating the intestinal barrier. The stronger the intestinal barrier defense and the less inflammation, the more beneficial it is for resistance to GBS colonization.Some lactic acid bacteria, such as *Lactobacillus rhamnosus* and *Lactobacillus plantarum*, have been shown to increase the expression of MUC in human intestinal cell lines Caco-2 and HT29, maintaining the integrity of the intestinal mucosa [57]; moreover, lactic acid bacteria can also upregulate the expression of E-cadherin and tight junctions (TJ) in IEC, competitively inhibiting the binding of bacteria to TJs, thereby suppressing the infection-induced increase in intestinal permeability, reducing inflammation, and protecting intestinal barrier function [58-59]. SCFAs also play an important role in regulating the integrity of the epithelial barrier. SCFAs can passively diffuse into cells, directly or indirectly affecting processes such as cell proliferation, differentiation, and gene expression [60]. *Bifidobacteria* can produce acetate in the colon, which promotes the expression of anti-inflammatory and anti-apoptotic genes in the intestinal epithelium, enhancing the integrity of the epithelial barrier. Butyrate, as the primary energy source for colonic cells, can nourish intestinal epithelial cells, promote the generation of IEC-derived MUC, and enhance the strength of TJs [60-62]. Short-chain fatty acids can maintain the integrity of the intestinal epithelium, preventing the leakage of GBS and lipopolysaccharides into the systemic circulation and their dissemination to the uterus, placenta, or amniotic cavity, thereby preventing the production of inflammatory mediators and prostaglandins induced by lipopolysaccharides. An increase in short-chain fatty acids in the intestine during pregnancy may remotely reduce the risk of spontaneous preterm birth associated with infection and inflammation [63]. These studies indicate that probiotics can promote the secretion of MUC, increase the TJs between adjacent epithelial cells, and positively regulate the intestinal barrier to help reduce the invasion and adhesion of pathogens such as GBS.

3.2.2 Immune Regulation

Components of probiotic cell walls (such as lipopolysaccharides, peptidoglycan, and β-glucans) can stimulate and train the host's immune system, modulating the intestinal mucosal immune system to

enhance the host's defense against GBS invasion [64]. Antimicrobial peptides produced by IEC and Paneth cells are important components of intestinal mucosal immunity. They primarily exploit the differences between bacterial and eukaryotic cell membranes to selectively target bacterial cell membranes and peptidoglycan layers, disrupting their integrity to achieve an antibacterial effect [56]. *Lactobacillus reuteri* can activate the Wnt/β-catenin pathway, leading to an increase in the expression of antimicrobial peptides [65]. The study by De Gregorio et al. [66] indicates that inoculating mice with *Lactobacillus rhamnosus* CRL1324 before GBS infection can reduce the number of pathogen-induced neutrophils and increase the number of activated macrophages. Additionally, inoculating with CRL1324 before GBS infection leads to an increase in B lymphocytes and IgA and IgG subclasses after infection.

SCFAs produced by probiotics play an important role in regulating the immune system and inflammatory responses. SCFAs can stimulate IECs to produce antimicrobial peptides (such as β-defensin and REG3γ) to maintain intestinal homeostasis [60]. Research has found that SCFAs help enhance the activity of colonic regulatory T cells, thereby reducing local intestinal inflammation [46]. Butyrate can increase the levels of the anti-inflammatory cytokine IL-10 in the colon and decrease the levels of the pro-inflammatory cytokines IL-6 and IL-1β[61].

3.3 The Impact of Antibiotics on Colonization Resistance

In the fight against infectious diseases, antibiotics are used to prevent and treat various bacterial infections, saving countless lives.However, excessive and prolonged use of antibiotics may have adverse effects, including changes in microbial species and numbers, bacterial antibiotic resistance, and the destruction of the intestinal mucus layer and TJs, which may reduce the intestinal colonization resistance to pathogenic bacteria, leading to excessive proliferation of pathogenic bacteria in the intestine[67].According to reports, intravenous antibiotics may lead to the development of resistance in GBS and other pathogenic bacteria, and they can disrupt the gut microbiota of newborns[50]. The recovery of microbial diversity in children after antibiotic treatment takes about one month. The administration of gentamicin, meropenem, and vancomycin reduces the number of *bifidobacteria*, a beneficial gut microbiota, in adults [33].

Changes in the composition of gut microbiota and the reduction in resistance to GBS colonization will increase susceptibility to GBS infection and the risk of reinfection.

4 Probiotic Applications

Live microorganisms that are beneficial to host health are called probiotics, also known as microecological preparations. Probiotics are part of the normal flora in the environment and can regulate the balance of intestinal flora through intestinal colonization resistance, preventing the excessive growth of pathogenic bacteria in the intestines and achieving the purpose of disease prevention and treatment.Current research has found that oral probiotics can alter the vaginal microbiota [48,68]. Oral administration of certain *Lactobacillus* strains, such as *Lactobacillus salivarius* [69], *Lactobacillus rhamnosus*, and *Lactobacillus reuteri* [70], can reduce the number of GBS-positive pregnant women in the rectum and vagina during pregnancy, thereby decreasing the number of pregnant women receiving antibiotic treatment during delivery. Some probiotics, such as *Lactobacillus*, *Bifidobacterium*, and *Clostridium butyricum*, have shown potential to inhibit GBS growth in vitro or in mouse models [42,71-78]. These studies indicate that symbiotic bacteria in the gut can inhibit the colonization and expansion of GBS in the gut through colonization resistance, reducing the seeding of GBS from the gut to the vagina, thereby lowering the rectal and vaginal GBS positivity rates during pregnancy and reducing the use of antibiotics.Currently, probiotic preparations come in various forms: heat-killed probiotics, cell-free supernatants of probiotics, purified specific components, or genetically engineered probiotics[79].Choosing probiotic strains that can effectively counteract GBS colonization in the gastrointestinal and urogenital tracts, and that are safe to use, can minimize the risk of maternal-fetal GBS infection and reduce the use of antibiotics.

5 Overview and Future Perspectives

Currently, the phenomenon of bacterial resistance and multidrug resistance is becoming increasingly common. GBS infections pose a significant disease burden on human health, particularly for pregnant women and newborns.In summary, the gut microbiota plays a crucial role in maintaining human health, serving as the core of intestinal colonization resistance and performing a dual function: producing inhibitory compounds (bacteriocins and fatty acids) that directly antagonize GBS growth and colonization; and inhibiting GBS adhesion and invasion through mechanisms such as positively regulating the intestinal barrier, competing for adhesion sites, and stimulating and training the innate immune system of the gut. If colonization resistance can be reasonably utilized to increase the intestinal antagonism against GBS colonization, it could reduce GBS colonization in the intestines of the population, especially in women of childbearing age, and decrease the occurrence of GBS spreading from the intestines to the reproductive tract. This is expected to lower the threat of GBS to the health of pregnant women and newborns from a primary prevention perspective. Gut microbiome consists of trillions of bacteria from hundreds of different species, making it very difficult to study the specific functions of probiotics in colonization resistance. The safe use and efficacy exploration of probiotics and prebiotics are currently major research hotspots. The complex network of interactions between GBS and gut microbiota, as well as the precise mechanisms of colonization resistance, are future research directions.

References

1. Raabe V N, Shane A L. Group B Streptococcus (*Streptococcus agalactiae*) [J]. Microbiol Spectr, 2019, 7(2): GPP3-0007-2018
2. Barkham T, Sheppard A, Jones N, et al. *Streptococcus agalactiae* that caused meningitis in healthy adults in 1998 are ST283, the same type that caused a food-borne outbreak of invasive sepsis in 2015: An observational molecular epidemiology study[J]. *Clin Microbiol Infect*, 2018, 24(8): 923-925
3. Kalimuddin S, Chen S L, Lim C T K, *et al*. 2015 Epidemic of severe *Streptococcus agalactiae* sequence type 283 infections in Singapore associated with the consumption of raw freshwater fish: A detailed analysis of clinical, epidemiological, and bacterial sequencing data[J]. *Clin Infect Dis*, 2017, 64(suppl_2): S145-s152.
4. Luangraj M, Hiestand J, Rasphone O, *et al*. Invasive *Streptococcus agalactiae* ST283 infection after fish consumption in two sisters, Lao PDR[J]. *Wellcome Open Res*, 2022, 7: 148.
5. Zwe Y H, Goh Z H E, Chau M L, *et al*. Survival of an emerging foodborne pathogen: Group B *Streptococcus* (GBS) serotype III sequence type (ST) 283-under simulated partial cooking and gastric fluid conditions[J]. *Food Sci Biotechnol*, 2019, 28(3): 939-944
6. Chau M L, Chen S L, Yap M, *et al*. Group B *Streptococcus* infections caused by improper sourcing and handling of fish for raw consumption, singapore, 2015-2016 [J]. *Emerg Infect Dis*, 2017, 23(12): 2002-10.
7. Graux E, Hites M, Martiny D, *et al*. Invasive group B *Streptococcus* among non-pregnant adults in BrusselsCapital Region, 2005-2019[J]. *Eur J Clin Microbiol Infect Dis*, 2021, 40(3): 515-523.
8. Wahid H H, Mustapha Rounal P F D, Bahez A, *et al*. A review of group B *Streptococcus* (GBS) vaginal colonization and ascending intrauterine infection: Interaction between host immune responses and gbs virulence factors[J]. *Acta Scientifica Malaysia*, 2022: 17-22.
9. Liu Y, Liu J. Group B *Streptococcus*: Virulence factors and pathogenic mechanism[J]. *Microorganisms*, 2022, 10(12): 2483.
10. Huang J, Lin X Z, Zhu Y, *et al*. Epidemiology of group B streptococcal infection in pregnant women and diseased infants in Mainland China[J]. *Pediatr Neonatol*, 2019, 60(5): 487-495
11. Cho C Y, Tang Y H, Chen Y H, *et al*. Group B streptococcal infection in neonates and colonization in pregnant women: An epidemiological retrospective analysis[J]. *J Microbiol Immunol Infect*, 2019, 52(2): 265-272.
12. Ferreira M B, de-Paris F, Paiva R M, *et al*. Assessment of conventional PCR and real-time PCR compared to the gold standard method for screening *Streptococcus agalactiae* in pregnant

women[J]. *Braz J Infect Dis*, 2018, 22(6): 449-454.
13. Brown A P, Denison F C. Selective or universal screening for GBS in pregnancy (review)[J]. *Early Hum Dev*, 2018, 126: 18-22.
14. Reid G, Bruce A W. Could probiotics be an option for treating and preventing urogenital infections?[J]. *Medscape Womens Health*, 2001, 6(5): 9.
15. Gomaa E Z. Human gut microbiota/microbiome in health and diseases: A review[J]. *Antonie van Leeuwenhoek*, 2020, 113(12): 2019-2040.
16. Bron P A, Kleerebezem M, Brummer R J, *et al*. Can probiotics modulate human disease by impacting intestinal barrier function?[J]. *Brit J Nutr*, 2017, 117(1): 93-107.
17. Buffie C G, Pamer E G. Microbiota-mediated colonization resistance against intestinal pathogens[J]. *Nat Rev Immun*, 2013, 13(11): 790-801.
18. Gao Y, Shang Q, Wei J, *et al*. The correlation between vaginal microecological dysbiosis-related diseases and preterm birth: A review[J]. *Med Microecol*, 2021, 8: 100043.
19. Yuan X Y, Liu H Z, Liu J F, *et al*. Pathogenic mechanism, detection methods and clinical significance of group B *Streptococcus*[J]. *Future Microbiol*, 2021, 16: 671-685.
20. Hickman M E, Rench M A, Ferrieri P, *et al*. Changing epidemiology of group B streptococcal colonization[J]. *Pediatrics*, 1999, 104(2 Pt 1): 203-209.
21. Tavares T, Pinho L, Bonifácio Andrade E. Group B streptococcal neonatal meningitis[J]. *Clin Microbiol Rev*, 2022, 35(2): e0007921.
22. Zhu Y, Lin X Z. Updates in prevention policies of earlyonset group B streptococcal infection in newborns[J]. *Pediatr Neonatol*, 2021, 62(5): 465-475.
23. Amabebe E, Anumba D O C. Female gut and genital tract microbiota-induced crosstalk and differential effects of short-chain fatty acids on immune sequelae[J]. *Front Immunol*, 2020, 11: 2184.
24. Korang S K, Safi S, Nava C, *et al*. Antibiotic regimens for early-onset neonatal sepsis[J]. *Cochrane Database Syst Rev*, 2021, 5(5): Cd013837.
25. Kuppala V S, Meinzen-Derr J, Morrow A L, *et al*. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants[J]. *J Pediatr*, 2011, 159(5): 720-725.
26. Cotten C M, Taylor S, Stoll B, *et al*. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants[J]. *Pediatrics*, 2009, 123(1): 58-66.
27. Cordero L, Ayers L W. Duration of empiric antibiotics for suspected early-onset sepsis in extremely low birth weight infants[J]. *Infect Control Hosp Epidemiol*, 2003, 24(9): 662-666.
28. Zimmermann P, Gwee A, Curtis N. The controversial role of breast milk in GBS late-onset disease[J]. *J Infect*, 2017, 74: S34-S40.
29. Li J, Liu L, Zhang H, *et al*. Severe problem of macrolides resistance to common pathogens in China[J]. *Front Cell Infect Microbiol*, 2023, 13: 1181633.
30. Weiss M E, Adkinson N F. Immediate hypersensitivity reactions to penicillin and related antibiotics[J]. *Clin Allergy*, 1988, 18(6): 515-540.
31. Hughes R C E, Williman J A, Gullam J E. Antenatal haemoglobin A1c centiles: Does one size fit all?[J]. *Aust N Z J Obstet Gynaecol*, 2018, 58(4): 411-416.
32. Jauréguy F, Carton M, Panel P, *et al*. Effects of intrapartum penicillin prophylaxis on intestinal bacterial colonization in infants[J]. *J Clin Microbiol*, 2004, 42(11): 5184-5188.
33. Shah T, Baloch Z, Shah Z, *et al*. The intestinal microbiota: impacts of antibiotics therapy, colonization resistance, and diseases[J]. *Int J Mol Sci*, 2021, 22(12): 6597.
34. Caballero-Flores G, Pickard J M, Núñez G. Microbiotamediated colonization resistance: Mechanisms and regulation[J]. *Nat Rev Microbiol*, 2023, 21(6): 347-360.
35. Zhang Y, Tan P, Zhao Y, *et al*. Enterotoxigenic *Escherichia coli*: Intestinal pathogenesis mechanisms and colonization resistance by gut microbiota[J]. *Gut Microbes*, 2022, 14(1): 2055943.
36. Cotter P D, Ross R P, Hill C. Bacteriocins - a viable alternative to antibiotics?[J]. *Nat Rev Microbiol*, 2013, 11(2): 95-105.

37. Rea M C, Sit C S, Clayton E, *et al*. Thuricin CD, a posttranslationally modified bacteriocin with a narrow spectrum of activity against *Clostridium difficile*[J]. *Proceed National Acad Sci*, 2010, 107(20): 9352-9357.
38. Hayes K, Cotter L, O'Halloran F. *In vitro* synergistic activity of erythromycin and nisin against clinical Group B *Streptococcus* isolates[J]. *J Appl Microbiol*, 2019, 127(5): 1381-1390.
39. Breukink E, Wiedemann I, van Kraaij C, *et al*. Use of the cell wall precursor lipid II by a pore-forming peptide antibiotic[J]. *Science*, 1999, 286(5448): 2361-2364
40. Bodaszewska-Lubas M, Brzychczy-Wloch M, Gosiewski T, *et al*. Antibacterial activity of selected standard strains of lactic acid bacteria producing bacteriocins-pilot study[J]. *Postepy Hig Med Dosw* (*Online*), 2012, 66: 787-794.
41. Ruíz F O, Gerbaldo G, García M J, *et al*. Synergistic effect between two bacteriocin-like inhibitory substances produced by *Lactobacilli* strains with inhibitory activity for *Streptococcus agalactiae*[J]. *Curr Microbiol*, 2012, 64(4): 349-356.
42. Ermolenko E I, Chernysh A, Martsinkovskaia I V, *et al*. Influence of probiotic enterococci on the growth of *Streptococcus agalactiae*[J]. *Zh Mikrobiol Epidemiol Immunobiol*, 2007(5): 73-77.
43. Shuster K A, Hish G A, Selles L A, *et al*. Naturally occurring disseminated group B *Streptococcus* infections in postnatal rats[J]. *Comp Med*, 2013, 63(1): 55-61.
44. Mélançon D, Grenier D. Production and properties of bacteriocin-like inhibitory substances from the swine pathogen *Streptococcus suis* serotype 2[J]. *Appl Environ Microbiol*, 2003, 69(8): 4482-4488.
45. Mota-Meira M, LaPointe G, Lacroix C, *et al*. MICs of mutacin B-Ny266, nisin A, vancomycin, and oxacillin against bacterial pathogens[J]. *Antimicrob Agents Chemother*, 2000, 44(1): 24-29.
46. Corrêa-Oliveira R, Fachi J L, Vieira A, *et al*. Regulation of immune cell function by short-chain fatty acids[J]. *Clin Transl Immunol*, 2016, 5(4): e73.
47. Alsharairi N A. The role of short-chain fatty acids in mediating very low-calorie ketogenic diet-infant gut microbiota relationships and its therapeutic potential in obesity[J]. *Nutrients*, 2021, 13(11): 3702.
48. Lai T J, Wang Y H, Chong E, *et al*. The impact of prenatal use of oral *Clostridium butyricum* on maternal group B *Streptococcus* colonization: A retrospective study[J]. *Taiwan J Obstet Gynecol*, 2021, 60(3): 442-448.
49. Muhammad A Y, Amonov M, Murugaiah C, *et al*. Intestinal colonization against *Vibrio cholerae*: Host and microbial resistance mechanisms[J]. *AIMS Microbiol*, 2023, 9(2): 346-374.
50. Marziali G, Foschi C, Parolin C, *et al*. *In vitro* effect of vaginal *Lactobacilli* against group B *Streptococcus*[J]. *Microbial Pathogenesis*, 2019, 136: 103692.
51. De Gregorio P R, Tomás M S J, Terraf M C L, *et al*. *In vitro* and *in vivo* effects of beneficial vaginal *Lactobacilli* on pathogens responsible for urogenital tract infections[J]. *J Med Microbiol*, 2014, 63(Pt 5): 685-696
52. Ducarmon Q R, Zwittink R D, Hornung B V H, *et al*. Gut microbiota and colonization resistance against bacterial enteric infection[J]. *Microbiol Mol Biol Rev*, 2019, 83(3): e00007-19.
53. Shabayek S, Spellerberg B. Group B streptococcal colonization, molecular characteristics, and epidemiology[J]. *Front Microbiol*, 2018, 9: 437.
54. Pietrocola G, Arciola C R, Rindi S, *et al*. *Streptococcus agalactiae* non-pilus, cell wall-anchored proteins: Involvement in colonization and pathogenesis and potential as vaccine candidates[J]. *Front Immunol*, 2018, 9: 602.
55. Nobbs A H, Lamont R J, Jenkinson H F. *Streptococcus* adherence and colonization[J]. *Microbiol Mol Biol Rev*, 2009, 73(3): 407-450.
56. Kim S, Covington A, Pamer E G. The intestinal microbiota: Antibiotics, colonization resistance, and enteric pathogens[J]. *Immunol Rev*, 2017, 279(1): 90-105.
57. Dudík B, Kiňová Sepová H, Bilka F, *et al*. Mucin precultivated *Lactobacillus reuteri* E shows enhanced adhesion and increases mucin expression in HT-29 cells[J]. *Antonie van Leeuwenhoek*, 2020, 113(8): 1191-1200.
58. Bai Y, Lyu M, Fukunaga M, *et al*. *Lactobacillus johnsonii* enhances the gut barrier integrity via

the interaction between GAPDH and the mouse tight junction protein JAM-2[J]. *Food Funct*, 2022, 13(21): 11021-11033.
59. Karczewski J, Troost F J, Konings I, *et al*. Regulation of human epithelial tight junction proteins by *Lactobacillus plantarum in vivo* and protective effects on the epithelial barrier[J]. *Am J Physiol Gastrointest Liver Physiol*, 2010, 298(6): G851-G859.
60. Parada Venegas D, De la Fuente M K, Landskron G, *et al*. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases[J]. *Front Immunol*, 2019, 10: 277.
61. Donohoe D R, Garge N, Zhang X, *et al*. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon[J]. *Cell Metab*, 2011, 13(5): 517-526.
62. Yan H, Ajuwon K M. Butyrate modifies intestinal barrier function in IPEC-J2 cells through a selective upregulation of tight junction proteins and activation of the Akt signaling pathway[J]. *PLoS One*, 2017, 12(6): e0179586.
63. Brokaw A, Furuta A, Dacanay M, *et al*. Bacterial and host determinants of group B streptococcal vaginal colonization and ascending infection in pregnancy[J]. *Front Cell Infect Microbiol*, 2021, 11: 720789.
64. Cortes-Perez N G, de Moreno de LeBlanc A, GomezGutierrez J G, *et al*. Probiotics and trained immunity[J]. *Biomolecules*, 2021, 11(10): 1402.
65. Ghanavati R, Asadollahi P, Shapourabadi M B, *et al*. Inhibitory effects of *Lactobacilli* cocktail on HT-29 colon carcinoma cells growth and modulation of the Notch and Wnt/β-catenin signaling pathways[J]. *Microbial Pathogenesis*, 2020, 139: 103829.
66. De Gregorio P R, Juárez Tomás M S, Nader-Macías M E. Immunomodulation of *Lactobacillus reuteri* CRL1324 on group B *Streptococcus* vaginal colonization in a murine experimental model[J]. *Am J Reprod Immunol*, 2016, 75(1): 23-35.
67. Jump R L, Polinkovsky A, Hurless K, *et al*. Metabolomics analysis identifies intestinal microbiota-derived biomarkers of colonization resistance in clindamycin-treated mice[J]. *PLoS One*, 2014, 9(7): e101267.
68. Borges S, Silva J, Teixeira P. The role of *Lactobacilli* andprobiotics in maintaining vaginal health[J]. *Arch Gynecol Obstet*, 2014, 289(3): 479-489.
69. Martín V, Cárdenas N, Ocaña S, *et al*. Rectal and vaginal eradication of *Streptococcus agalactiae* (GBS) in pregnant women by using *Lactobacillus salivarius* CECT 9145, a target-specific probiotic strain[J]. *Nutrients*, 2019, 11(4): 810.
70. Ho M, Chang Y Y, Chang W C, *et al*. Oral *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 to reduce group B *Streptococcus* colonization in pregnant women: A randomized controlled trial[J]. *Taiwan J Obstet Gynecol*, 2016, 55(4): 515-518.
71. Açikgöz Z C, Gamberzade S, Göçer S, *et al*. Inhibitor effect of vaginal lactobacilli on group B streptococci[J]. *Mikrobiyol Bul*, 2005, 39(1): 17-23.
72. Bodaszewska M, Brzychczy-Włoch M, Gosiewski T, *et al*. Evaluation of group B streptococcus susceptibility to lactic acid bacteria strains[J]. *Med Dosw Mikrobiol*, 2010, 62(2): 153-161.
73. Marsalková S, Cízek M, Vasil M, *et al*. Testing two *Lactobacillus plantarum* and *Lactobacillus acidophilus* strains for their suitability as a lipoid probiotic[J]. *Berl Munch Tierarztl Wochenschr*, 2004, 117(3-4): 145-147.
74. Patras K A, Wescombe P A, Rösler B, *et al*. *Streptococcus salivarius* K12 limits group B *Streptococcus* vaginal colonization[J]. *Infect Immun*, 2015, 83(9): 3438-3444.
75. De Gregorio P R, Juárez Tomás M S, Leccese Terraf M C, *et al*. Preventive effect of *Lactobacillus reuteri* CRL1324 on group B *Streptococcus* vaginal colonization in an experimental mouse model[J]. *J Appl Microbiol*, 2015, 118(4): 1034-1047.
76. Aloisio I, Mazzola G, Corvaglia L T, *et al*. Influence of intrapartum antibiotic prophylaxis against group B *Streptococcus* on the early newborn gut composition and evaluation of the anti-*Streptococcus* activity of bifidobacterium strains[J]. *Appl Microbiol Biotechnol*, 2014, 98(13): 6051-6060.
77. Tsapieva A, Duplik N, Suvorov A. Structure of plantaricin locus of *Lactobacillus plantarum* 8P-

A3[J]. *Benef Microbes*, 2011, 2(4): 255-261.
78. Zárate G, Nader-Macias M E. Influence of probiotic vaginal *Lactobacilli* on *in vitro* adhesion of urogenital pathogens to vaginal epithelial cells[J]. *Lett Appl Microbiol*, 2006, 43(2): 174-180.
79. Cuevas-González P F, Liceaga A M, Aguilar-Toalá J E.Postbiotics and paraprobiotics: From concepts to applications[J]. *Food Res Int*, 2020, 136: 109502.