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Gut-lung cross talk in COVID-19 pathology and fatality rate

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1. Introduction

Recent developments in microbiota studies have led to a better understanding of the impact of populations of commensal microbiota within the human body. The role of the gut microbiota in health and diseases is being progressively studied; nevertheless, it still needs more understanding [1]. Microbes that inhabit both the gut and the lung live in a mutualistic relationship within the host. Among the relevant interorgan connections, the gut-lung axis remains less studied when compared with other axes such as the gut-brain axis [1].

Coronaviruses are a large group of viruses that infect mammals and birds [2,3]. Respiratory syndromes caused by Coronaviruses can range from signs similar to common colds to severe pneumonia; fortunately, for the vast majority of affected individuals, the symptoms are minor, and people tend to improve within a few days following the appearance of the symptoms [4].

In December 2019, a new type of Coronavirus associated with the development of cases of pneumonia and mortality emerged in the city of Wuhan, China, and quickly spread out to be a global pandemic outbreak [5,6]. This new Coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), based on its genetic similarities to SARS-CoV (the virus identified in 2002 as the cause of severe acute respiratory syndrome), has been originally linked to a food market in Wuhan dealing with live animal and seafood [7].

Chinese medicine considers the lung and the gut as a pair of linked organ systems (*Biao-Li*). The relation of the lung and gut is commonly affected by internal and external interactions [8]. There is a notion suggesting that lung diseases are often associated with colon disorders and vice versa. The mechanism is complex, where genetic, environmental, and immunologic factors contribute to many cellular and molecular events [9]. From a pathologic point of view, the microscopic hallmark of inflammatory bowel disease in the

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bowel and the lungs is the penetration of chronic inflammatory cells and the response of interstitial cells. Studies of gut microbiota have shown that microbiota could provide essential health benefits to the host by regulating immune homeostasis [10].

Chronic lung syndromes, such as chronic obstructive pulmonary disease, cystic fibrosis, and asthma, display signs of intestinal dysfunction [11–13]. In addition, respiratory viral infections frequently demonstrate concomitant intestinal dysfunction [14,15]. It has also been shown that alterations in the gut microenvironment are usually reported during the development of various lung diseases. Among these alterations is the shift in the composition of the gut bacteria or microbiota [16–18].

It is well accepted that probiotics can minimize antibiotic-associated dysbiosis and infections not only in the gastrointestinal tract but also in other body sites, including in respiratory tract infections (RTIs) [19,20]. Probiotics are generally safe and noninvasive, even in the most susceptible populations including intensive-care patients [21]. The use of probiotics, prebiotics, and synbiotics could produce protective effects against external environmental viral infections through the buildup of internal defenses by boosting the immune system. In the case of coronavirus disease 2019 (COVID-19) pandemic, this might result in reduced infection rates, lessened systemic inflammatory responses, shorter intensive-care stays and mechanical ventilation duration, and lower fatality [21].

The evidence is highly suggestive of a dynamic cross talk between the gut and the lungs as two mucosa covered parts of the human body. In this chapter, we discuss the changes in the gut microbial composition associated with lung disease and the impact of altered gut microbiota on healthy and COVID-19-infected lungs, together with the possibility of using probiotic co-supplementation with current therapies as a protective strategy in COVID-19 patients, which might help flatten the curve of infection.

2. Adult human gut microbiota

The human body is normally colonized by trillions of bacteria in different compartments of the body. Among these compartments are the oral cavity, the gut, and the respiratory tract [9–16]. The colonizing bacteria are usually from six different phyla: Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria, and Cyanobacteria [22–28]. However, the relative abundance and diversity of these phyla, especially the bacterial composition at the genera level, vary considerably between different body compartments [29].

A healthy adult's gut microbiome is an extraordinarily stable microbial community composed of highly adapted microbial species [30] that are affected by the environment as well as the host genetics [31]. While high microbiota diversity appears to be associated with health, a dynamic loss of diversity may be prognostic of increased disease risk [32,33]. A physically inactive lifestyle and the consumption of a diet that is high in refined carbohydrates and salt and low in dietary fibers [34,35] are connected to the depletion of healthy gut microbiota and increased prevalence of chronic diseases [36].

Dysbiosis of the gut microbiota has been associated with a variety of local and systemic chronic disorders, highlighting the importance of a balanced microbial community in the gut for proper immune function and health [37,38]. Keeping a balanced gut microbiota, or restoring an altered gut flora, can be accomplished through different strategies, among which are probiotics, fecal microbiota transplantation (FMT), or live biotherapeutics. This may help in the development of a healthy and functional gut microbiota, a normal immune response, and healthy organs through multiple gut microbiota, brain, liver, and retina axis [1,39] (see Fig. 3.1).

3. Respiratory tract microbiota

Recently, with the introduction of the culture-independent procedures for microbiologic examinations, which are based on RNA/DNA sequencing or microarrays, many studies indicated that, in addition to the upper respiratory tract, the lower respiratory tract, i.e., the lungs, is populated by various types of microbiota [40,41].

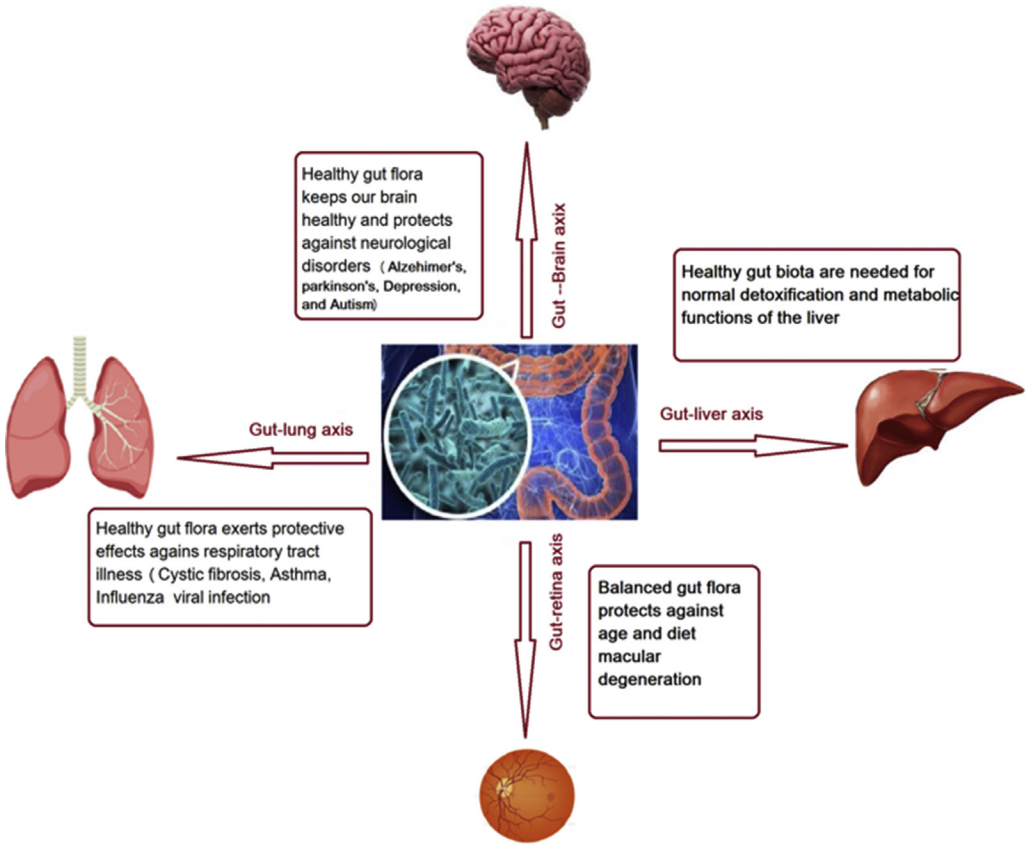

FIGURE 3.1 Importance of healthy and functional gut microbiota for the maintenance of healthy organs through gut-brain, liver, lung, and retina axis.

However, the lower respiratory tract is one of the least colonized by bacteria among compartments of the human body. In a marked similarity to the gut, the two predominant phyla identified in the respiratory tract are Firmicutes and Bacteroidetes, whereas Actinobacteria, Proteobacteria, and Fusobacteria are minor constituents of the respiratory tract microbiota [23,25]. The "core microbiota" of healthy individuals consists mainly of the following genera: *Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacterium*, *Veillonella*, *Haemophilus*, *Neisseria*, and *Porphyromonas* [42,43]. A study provided evidence indicating that gut and lung microbiota develop simultaneously and that there is a constant cross talk between these two compartments [44].

It has been shown that bacteria appear in the gut earlier than their identification in the airway [44], providing suggestive evidence for the involvement of microaspiration of gut microbes in the development of the lung microbiota. Factors such as diet have also been shown to affect the composition of the gut and lung microbiota [44,45]. The diversity of lung microbiota is mostly affected by three factors: the type and number of microbiota arriving into the lungs, removal of microbes from the lungs, and replication rates of the microbe itself in the lungs [43,46].

4. Gut-lung cross talk during viral COVID-19

Based on the recently highlighted role of gut microbiota in health and diseases, it is essential to clarify the role of gut-lung cross talk in the etiopathology of lung disease [47]. The cross talk between gut microbiota and lungs, known as the gut-lung axis, is critically important for the homeostasis and immune response of the respiratory system. Certain gut microbiota-associated strategies have been approved to treat and prevent lung diseases [1]. Ichinohe et al. [48] suggested that gut microbiota play a critical role in the generation of virus-specific $CD4^+$ and $CD8^+$ T cells and antibody responses after a respiratory influenza virus infection. Multiple studies have shown that alterations in the gut bacterial species and metabolites were associated with abnormal immune responses, inflammation, and lung disease severity. Altered gut microbiota composition can be related to lung disease through the gut-lung axis. Regulatory T-cell (Treg) subsets, toll-like receptors (TLRs), inflammatory cytokines, surfactant protein D, and several other factors have been postulated as contributors to the causal mechanisms [49–54].

The effect of gut microbiota alterations on respiratory viral infections has been studied in the recent years [55–57]. Reduction in the diversity of the gastrointestinal tract microbiota was followed by a considerable increase in mortality due to respiratory viral infections. This increase in mortality due to respiratory viral infections was associated with a defective immune response characterized by increased lung interferon (IFN)-γ, interleukin (IL)-6, and CCL2 and decreased count of Tregs in the lungs. Neutralization of IFN-γ or adoptive transfer of Tregs significantly combated the increased mortality [58]. Viral lung infections are also associated with an increase in colonic Muc5ac levels and fecal lipocalin-2, indicating low-grade inflammation in the gut (Fig. 3.2) [59].

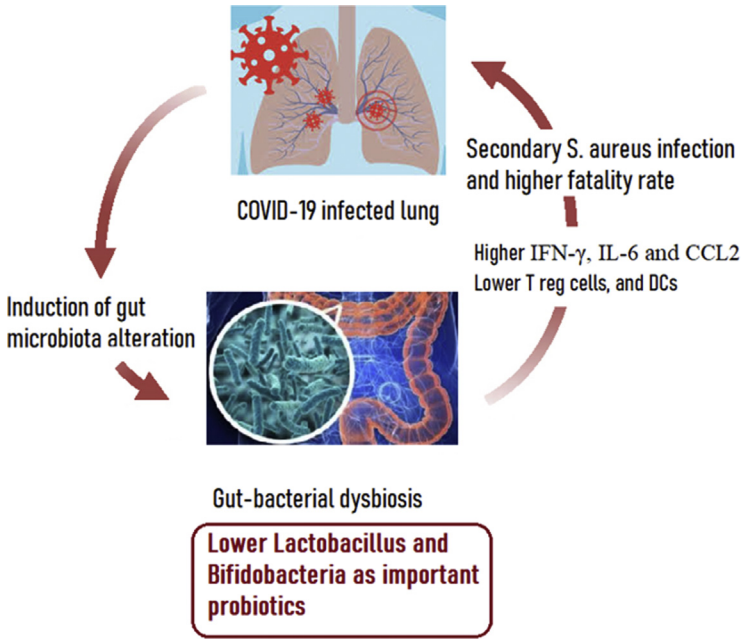

FIGURE 3.2 Suggested gut microbiota-lung cross talk during coronavirus disease 2019 (COVID-19). *DCs*, dendritic cells; *IFN-γ*, interferon γ; *IL-6*, interleukin 6; *Tregs*, regulatory T cells.

Some patients with COVID-19 presented with dysbiosis of gut microbiota with decreased healthy bacteria or probiotics such as *Lactobacillus* and *Bifidobacterium*. Based on this finding, nutritional and gastrointestinal functions should be evaluated for all patients. Nutritional intervention through the use of prebiotics or probiotics is encouraged to regulate the balance of intestinal microbiota and thus reduce the risk of secondary infections due to bacterial translocation. Regular follow−up of fecal microbiota in patients during the 2-week quarantine is recommended and might help avoid secondary bacterial infection [60]. A study by Yu et al. [61] reported the dynamic structure of the host immune system and the gut microbiota imbalance in three critical care patients with COVID-19. Hypoxemia severity was correlated to the vicious circle between immune deficiency and gut microbiota imbalance and was suggested as a contributor to the high risk of fatal pneumonia.

On the other hand, several probiotics have been shown to prevent and/or decrease the length of viral infections. Most of the studies supporting the effectiveness of immune system reinforcement by using probiotics have been validated in animal models. In mice, intranasal injection of *Lactobacillus reuteri* or *Lactobacillus plantarum* have displayed a protective potential against lethal viral pneumonia [62].

The mechanism by which gut microbiota protect the lungs from *S. aureus* infection has been explored. Gut microbiota disruption caused by antibiotics decreased pulmonary resistance to *S. aureus* due to impaired TLR4 function [54].

Qin et al. [63] reported that severe COVID-19 cases have lower lymphocyte counts, higher leukocyte counts, and higher neutrophil/lymphocyte-ratio, as well as elevated levels of inflammatory cytokines. They also demonstrate much lower numbers of helper T cells and suppressor T cells. The percentage of naive helper T cells was increased and that of memory helper T cells was decreased in severe cases. Patients with COVID-19 also have lower levels of Treg cells that is correlated with the severity of the case. Thus these markers might help in the early diagnosis and, thereby, better management of novel Coronavirus infections.

5. Suggested COVID-19 intervention strategies through the use of probiotics and prebiotics

Extensive, and frequently improper, use of antibiotics may lead to the increase in bacterial resistance and disruption of the normal balance of human microbiota, thereby assisting pathogenic bacteria colonization [64,65]. Probiotics are defined by the World Health Organization as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [66]. The most commonly used probiotics are *Lactobacillus* and *Bifidobacterium* species, followed by the genera *Propionibacterium*, *Bacillus*, *Streptococcus*, *Enterococcus*, and *Escherichia coli* [67]. In addition, some yeast species are used as probiotics; for example, *Saccharomyces boulardii* and *Saccharomyces cerevisiae* are repeatedly used to treat gastrointestinal disorders [68,69]. A well-characterized probiotic should be defined clearly by the genus, species, and strain description, as well as specify the bacteriologic culture conditions [68]. Probiotic-containing products may be supplied as capsules, tablets, and most commonly as powders, as well as food ingredients [70].

Probiotics may exert a wide range of favorable effects, such as balancing the host gut microbiota and strengthening the innate and adaptive immune system, which may stimulate the development of resistance against pathogens [71]. It must be stated that probable major mechanisms of probiotic effects on RTIs are yet to be clearly defined. Besides the local effect of competitively inhabiting the gut to eliminate pathogenic bacterial species, controlling the gut barrier utility and permeability, probiotics have been shown to demonstrate numerous host immunomodulatory effects [72–74]. It has been shown that probiotics can influence both innate and adaptive immune responses by producing exopolysaccharides [75]. In addition, probiotics could increase leukocyte, neutrophil, and natural killer cell counts and activity [19]. They are also able to increase the expression of IL-10 and decrease inflammatory cytokine expression, such as tumor necrosis factor α, IL-1β, and IL-8 [76]. Furthermore, probiotics can maintain higher levels of salivary immunoglobulin A and produce bacteriocins and reuterin, which have antimicrobial activity [77] (see Fig. 3.3).

Data generated through a meta-analysis of 23 randomized clinical trials proposed that probiotic feeding may decrease the prevalence and disease duration of RTI episodes.

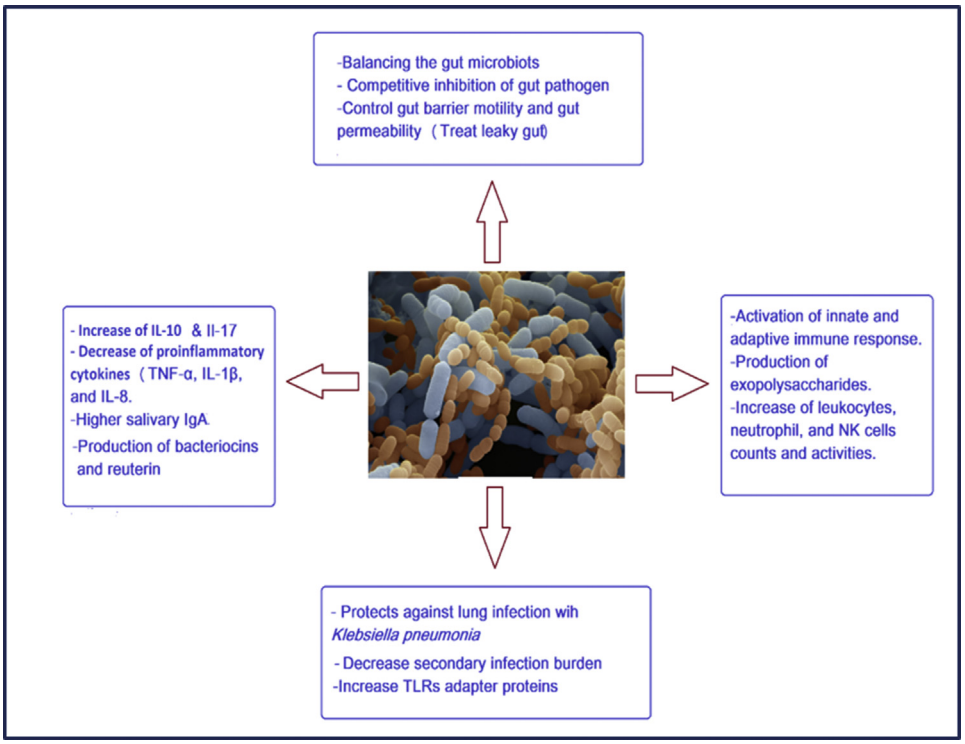

FIGURE 3.3 Different reported mechanisms of the favorable effects of probiotic supplementation. *IgA*, immunoglobulin A; *IL*, interleukin; *NK*, natural killer; *TLR*, toll-like receptor; *TNF-α*, tumor necrosis factor α.

It is essential to observe, in future clinical trials, the optimum probiotic strain(s), dosing, type of formulation, and time of intervention as well as implement an appropriate follow-up protocol [78].

Clinically used probiotics have been classified as monostrain or multistrain products, with multistrain/multispecies products being more beneficial because of the expected symbiosis among strains [79]. In addition to orally supplemented probiotics, fecal transplant can be used as another strategy of probiotic microbial intervention. Fecal microbial transplantation (FMT) denotes to the process of transferring gut microbiota from a healthy individual to a dysbiotic patient with unbalanced gut microbiota in an attempt to restore normal diversity of gut microbiota [80,81]. It is based on the rationale that manipulation of the microbiome could prove potentially therapeutic for disease states with an altered microbial composition.

A meta-analysis of clinical trials, involving more than 10,000 individuals, demonstrated that synbiotic (mixture of probiotic and prebiotic) interventions could be an alternative nutritional strategy for conferring human health and preventing RTIs. Future investigations on the clinical efficacy and safety of synbiotic interventions are necessary, with special attention to strain-specific and dose-specific measures [82]. A probiotic

Bifidobacterium longum 5(1A) was able to protect mice against lung infection caused by *Klebsiella pneumoniae*. It induced faster resolution of inflammation by increased production of IL-10 and decreased lung injury with significant decrease in the burden of secondary bacterial infection. The underlying mechanism is partly attributed to the activation of the TLR adapter protein [83].

Probiotics were able to produce a considerable reduction in the frequency of upper RTI in preschool Malaysian children. In a 10-month randomized, double-blind, parallel, placebo-controlled study, the effects of *B. longum* BB536 probiotic on upper RTI and diarrhea in 219 subjects (110 placebo and 109 BB536 supplemented) were evaluated [84]. While BB536 probiotic supplement did not exert significant effects against diarrhea in children, it was effective in reducing sore throat duration by 46%, fever by 27%, runny nose by 15%, and cough by 16% when compared to the placebo. Additionally, the probiotic-treated group demonstrates much higher abundance of the genus *Faecalibacterium* known to exert anti-inflammatory and immunomodulatory properties. Overall, the BB536 probiotic imparts protective effects against upper respiratory illnesses as well as beneficial gut microbiota modulating properties.

The effectiveness of using synbiotics in treating RTIs was reported to be a more potent preventive measure among adults than infants and children [85].

Using mice as a model system in microbiota research is still considered a powerful tool. In a rodent model, the microbiota can be examined under controlled conditions such as homogenous genetic background, diet consumption, and housing factors [86]. Feeding mice with probiotic *Lactobacillus paracasei* CNCM I-1518 strain resulted in reduced vulnerability to the influenza infection, concomitant with less accumulation of inflammatory cells in the lungs, earlier viral clearance, and overall improved health. Interestingly, *Allobaculum* (bacterial genus), known to be positively correlated with IL-17 expression, was significantly increased in *L. paracasei*-fed mice 7 days after influenza infection, even if the gut microbiota composition was not altered overall. *L. paracasei*-purified peptidoglycans partially represent the protective phenotype observed with *L. paracasei* [87,88].

It is well accepted that, when antibiotics are used, strengthening of gut microbiota by using probiotics will lessen the vulnerability to secondary infections as commonly happens in COVID-19 patients. In addition to the effectiveness of probiotics in treating RTIs, they are proposed to have a direct effect on SARS-CoV-2 or COVID-19. In fact, in line with the gut-lung cross talk, which has been anticipated to play a critical role in COVID-19 pathogenesis, controlled randomized trials showed that critically ill patients on mechanical ventilation who were given probiotics (*Lactobacillus rhamnosus* GG, live *Bacillus subtilis*, and *Enterococcus faecalis*) developed substantially less ventilator-associated pneumonia (VAP) compared with placebo [9,89,90]. This finding might contribute significantly to reducing the fatality rate of COVID-19 pandemic.

Chinese COVID-19 patients demonstrated microbial dysbiosis with diminished *Lactobacillus* and *Bifidobacterium* gut flora as a comorbidity in COVID-19 [60]. Lactobacilli and Bifidobacteria are the only two types of beneficial bacteria that were

accepted for combating COVID-19 through the restoration of healthy gut microbiota. Random use of conventional probiotics for COVID-19 management is not recommended until a clear understanding of the pathogenesis of SARS-CoV-2 and its effect on gut microbiota is attained. It is likely that a novel and more precise targeted approach to the modulation of gut microbiota will be accepted as one of the therapeutic mechanisms to combat COVID-19 and its comorbidities [89].

6. The role of probiotic in ventilator-associated pneumonia

The use of probiotics is an interesting emerging field in oral healthcare. Probiotics are defined as living microbial agents of human origin able to tolerate the hostile gastrointestinal environment to confer health benefits on the host when used in an adequate amount [66]. Probiotics have several positive effects on the health of the host, such as reduced constipation, decreased blood cholesterol levels, and improved lactose tolerance and calcium intake [91]. Probiotic bacteria consist of two main groups, namely, *Lactobacillus* and *Bifidobacterium*. *Lactobacillus*, as a member of oral microbial flora, can play an important role in the microcosm balance of the oral cavity. On the other hand, less information is available about the useful role of *Bifidobacterium* in the health of the oral cavity [92].

The widespread oral intake of probiotics as preventive and therapeutic products for gastrointestinal health makes them of considerable interest for oral healthcare workers [93]. Probiotics are recognized as a potent therapeutic agent for dental caries, periodontal disease, and halitosis. The oral cavity is a habitat for a diverse population of microorganisms that is responsible for influencing oral health and disease. Although resident oral microorganisms are typically in homeostasis with the host, a disturbance in the balance (e.g., decrease in oral pH, presence of high levels of dietary carbohydrates, and poor oral hygiene) can initiate and potentiate oral diseases such as dental caries, periodontitis, and gingivitis [94,95].

Studies have presented possible mechanisms behind the positive effect of probiotics on caries and dental plaque. Probiotics compete with pathogenic bacteria that adhere to the mucosa and tooth structure causing their displacement [96,97]; they produce hydrogen peroxide, lactic acid, and bacteriocin as antibacterial agents against oral pathogens [98–101]; they change the acidity of the oral environment by reducing the pH and thereby prevent the growth of bacteria [102]; and they stimulate nonspecific immunity and regulate cellular and humoral immune responses [103]. Probiotics also act as antioxidants and prevent plaque formation by neutralizing free electrons [104].

Although probiotic research in the field of dental sciences is relatively new, preliminary evidence suggests their beneficial influence on maintaining oral health. A literature review concluded that a potent probiotic helps prevent and reduce the risk of caries development in children and adults. *Lactobacillus* and *Streptococcus* species were examined for their anticariogenic potential in most of the studies [105]. Other studies

suggested that consumption of products containing probiotic lactobacilli or bifidobacteria can reduce the number of *Streptococcus mutans* in saliva and therefore could have a preventive effect on the development of dental caries [92,106–108]. On the other hand, Gruner et al. [109] evaluated the influence of probiotic therapy with lactobacilli on periodontal pathogen counts and concluded that the current evidence is insufficient for recommending probiotics for managing dental caries, but supportive toward managing gingivitis or periodontitis. Probiotics lower the pH of the oral cavity and prevent the formation of dental plaque and calculus that causes periodontal disease [110]. In addition, probiotics produce antioxidants that interfere with plaque formation by neutralizing the free electrons needed for mineral formation [111]. Probiotic mouthwash formulation was evaluated as an alternative to traditional mouthwash for the prevention of periodontal disease. It demonstrated a significant decrease in the plaque index and gingival index compared to placebo [112] and to chlorhexidine (CHX) [113–115].

Regular use of probiotics can also help control halitosis. The common organisms involved in halitosis are *Fusobacterium nucleatum, Porphyromonas gingivalis, Prevotella intermedia*, and *Treponema denticola*. These organisms degrade amino acids that are in turn transformed into volatile sulfur compounds causing halitosis. The use of *Weissella cibaria* as a mouthwash resulted in reduced levels of volatile sulfide components produced by *F. nucleatum* through the release of hydrogen peroxide and bacteriocin by *W. cibaria* that inhibited the proliferation of *F. nucleatum* [116]. *Streptococcus salivarius* also suppresses volatile sulfide compounds by competing for colonization areas with volatile sulfide-producing species [117].

VAP continues to be one of the most prevalent and serious complications during ventilation. Because of the high morbidity and mortality rate in VAP, pharmacologic and nonpharmacologic interventions aimed at VAP prevention have been proposed, including administration of antibiotics, selective digestive tract decontamination, CHX mouthwash, subglottic secretion drainage, elevation of the head of the bed, and other preventive measures [118–120]. Decontamination with antibiotics reduces the incidence of VAP [121], but it is not currently recommended due to the risk of development of resistant bacteria. Oropharyngeal rinse with CHX has been shown to be effective in reducing tracheal colonization and VAP incidence [122–124]; however, it does not influence the survival rate [122,124]. Nevertheless, similar to antibiotics, CHX induces bacterial resistance and hypersensitivity [125–127]. Although the effect of probiotics in VAP is still uncertain, several advantages such as low cost, ease of administration, and minimal toxicity make them a promising approach to prevent RTIs. Probiotics have been initially used as a potential adjunctive treatment for VAP prevention [128]. Later, some evidence emerged suggesting using it as a feasible and safe agent for oral care in critically ill patients to reduce pathogens in the oropharynx [129–134], while others failed to show any evidence to support reduction of ICU or hospital mortality by the administration of probiotics [132,135–137]. Probiotics could potentially reduce the incidence of pneumonia in critically ill patients by reducing the overgrowth of pathogenic microorganisms, enhancing gut barrier function, reducing bacterial translocation, and upregulation

of immune functions [103,138–143]. The effect of probiotics on VAP prevention is a controversial issue because the availability of high-quality randomized control trials is limited and their results are inconsistent [90,131,134,144–147].

The use of probiotics is an interesting emerging field in oral healthcare. Based on the currently available clinical data, it seems that dietary probiotics do not induce a major risk for oral health. Therefore probiotic therapy can be considered as a natural and noninvasive way to prevent tracheal colonization with pathogenic bacteria and reduce the risk of aspiration of contaminated secretions. However, high-quality randomized clinical trials with long-term follow-up are needed to confirm the clinical benefit of probiotics in critically ill patients.

References

[1] J.Y. Tan, Y.C. Tang, J. Huang, Gut microbiota and lung injury, Adv. Exp. Med. Biol. 1238 (2020) 55–72.

[2] S. Su, G. Wong, W. Shi, J. Liu, A.C. Lai, J. Zhou, et al., Epidemiology, genetic recombination, and pathogenesis of coronaviruses, Trends Microbiol. 24 (6) (2016) 490–502.

[3] S.R. Weiss, J.L. Leibowitz, Coronavirus pathogenesis, in: Advances in Virus Research, Elsevier, 2011, pp. 85–164.

[4] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513.

[5] World Health Organization, WHO Director-General's Remarks at the Media Briefing on 2019-nCoV on 11 February 2020, International World Health Organization, 2020.

[6] D. Cucinotta, M. Vanelli, WHO declares COVID-19 a pandemic, Acta Bio-Medica Atenei Parm 91 (1) (2020, 19) 157–160.

[7] C. Leung, Clinical features of deaths in the novel coronavirus epidemic in China, Rev. Med. Virol. 30 (3) (2020) e2103.

[8] J.-X. Ni, S.-H. Gao, Understanding the viscera-related theory that the lung and large intestine are exterior-interiorly related, J. Tradit. Chin. Med. 32 (2) (2012) 293–298.

[9] J. Zeng, C.-T. Wang, F.-S. Zhang, F. Qi, S.-F. Wang, S. Ma, et al., Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial, Intensive Care Med. 42 (6) (2016) 1018–1028.

[10] H. Chung, D.L. Kasper, Microbiota-stimulated immune mechanisms to maintain gut homeostasis, Curr. Opin. Immunol. 22 (4) (2010) 455–460.

[11] V. Baral, G. Connett, Acute intestinal obstruction as a presentation of cystic fibrosis in infancy, J. Cyst. Fibros. 7 (4) (2008) 277–279.

[12] S. Keely, P.M. Hansbro, Lung-gut cross talk: a potential mechanism for intestinal dysfunction in patients with COPD, Chest 145 (2) (2014) 199–200.

[13] A. Roussos, P. Koursarakos, D. Patsopoulos, I. Gerogianni, N. Philippou, Increased prevalence of irritable bowel syndrome in patients with bronchial asthma, Respir. Med. 97 (1) (2003) 75–79.

[14] C. Dilantika, E.R. Sedyaningsih, M.R. Kasper, M. Agtini, E. Listiyaningsih, T.M. Uyeki, et al., Influenza virus infection among pediatric patients reporting diarrhea and influenza-like illness, BMC Infect. Dis. 10 (1) (2010) 3.

[15] J. Wang, F. Li, H. Wei, Z.-X. Lian, R. Sun, Z. Tian, Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell−dependent inflammation, J. Exp. Med. 211 (12) (2014) 2397−2410.

[16] T.R. Abrahamsson, H.E. Jakobsson, A.F. Andersson, B. Björkstén, L. Engstrand, M.C. Jenmalm, Low gut microbiota diversity in early infancy precedes asthma at school age, Clin. Exp. Allergy 44 (6) (2014) 842−850.

[17] H. Bisgaard, N. Li, K. Bonnelykke, B.L.K. Chawes, T. Skov, G. Paludan-Müller, et al., Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age, J. Allergy Clin. Immunol. 128 (3) (2011) 646−652.

[18] E. Bruzzese, M.L. Callegari, V. Raia, S. Viscovo, R. Scotto, S. Ferrari, et al., Disrupted intestinal microbiota and intestinal inflammation in children with cystic fibrosis and its restoration with Lactobacillus GG: a randomised clinical trial, PLoS One 9 (2) (2014) e87796.

[19] E. Guillemard, J. Tanguy, A. Flavigny, S. de la Motte, J. Schrezenmeir, Effects of consumption of a fermented dairy product containing the probiotic *Lactobacillus casei* DN-114 001 on common respiratory and gastrointestinal infections in shift workers in a randomized controlled trial, J. Am. Coll. Nutr. 29 (5) (2010) 455−468.

[20] H. Szajewska, M. Kołodziej, D. Gieruszczak-Białek, A. Skórka, M. Ruszczyński, R. Shamir, Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG for treating acute gastroenteritis in children − a 2019 update, Aliment. Pharmacol. Ther. 49 (11) (2019) 1376−1384.

[21] J.M. Davison, P.E. Wischmeyer, Probiotic and synbiotic therapy in the critically ill: state of the art, Nutrition 59 (2019) 29−36.

[22] P.B. Eckburg, E.M. Bik, C.N. Bernstein, E. Purdom, L. Dethlefsen, M. Sargent, et al., Diversity of the human intestinal microbial flora, Science 308 (5728) (2005) 1635−1638.

[23] J.R. Erb-Downward, D.L. Thompson, M.K. Han, C.M. Freeman, L. McCloskey, L.A. Schmidt, et al., Analysis of the lung microbiome in the "healthy" smoker and in COPD, PLoS One 6 (2) (2011).

[24] D.N. Frank, L.M. Feazel, M.T. Bessesen, C.S. Price, E.N. Janoff, N.R. Pace, The human nasal microbiota and *Staphylococcus aureus* carriage, PLoS One 5 (5) (2010).

[25] M. Hilty, C. Burke, H. Pedro, P. Cardenas, A. Bush, C. Bossley, et al., Disordered microbial communities in asthmatic airways, PLoS One 5 (1) (2010).

[26] T.K. Kim, S.M. Thomas, M. Ho, S. Sharma, C.I. Reich, J.A. Frank, et al., Heterogeneity of vaginal microbial communities within individuals, J. Clin. Microbiol. 47 (4) (2009) 1181−1189.

[27] V. Lazarevic, K. Whiteson, S. Huse, D. Hernandez, L. Farinelli, M. Øster\aas, et al., Metagenomic study of the oral microbiota by Illumina high-throughput sequencing, J. Microbiol. Methods 79 (3) (2009) 266−271.

[28] A. Maldonado-Contreras, K.C. Goldfarb, F. Godoy-Vitorino, U. Karaoz, M. Contreras, M.J. Blaser, et al., Structure of the human gastric bacterial community in relation to *Helicobacter pylori* status, ISME J. 5 (4) (2011) 574−579.

[29] I. Cho, M.J. Blaser, The human microbiome: at the interface of health and disease, Nat. Rev. Genet. 13 (4) (2012) 260−270.

[30] D.A. Antonopoulos, S.M. Huse, H.G. Morrison, T.M. Schmidt, M.L. Sogin, V.B. Young, Reproducible community dynamics of the gastrointestinal microbiota following antibiotic perturbation, Infect. Immun. 77 (6) (2009) 2367−2375.

[31] V.K. Gupta, S. Paul, C. Dutta, Geography, ethnicity or subsistence-specific variations in human microbiome composition and diversity, Front. Microbiol. 8 (2017) 1162.

[32] J. Lloyd-Price, G. Abu-Ali, C. Huttenhower, The healthy human microbiome, Genome Med. 8 (1) (2016) 1−11.

[33] S. Lohner, D. Küllenberg, G. Antes, T. Decsi, J.J. Meerpohl, Prebiotics in healthy infants and children for prevention of acute infectious diseases: a systematic review and meta-analysis, Nutr. Rev. 72 (8) (2014) 523–531.

[34] D. Campbell-Lendrum, A. Prüss-Ustün, Climate change, air pollution and noncommunicable diseases, Bull. World Health Organ. 97 (2) (2019) 160.

[35] J. Fedacko, T. Takahashi, R.B. Singh, D. Pella, S. Chibisov, K. Hristova, et al., Globalization of diets and risk of noncommunicable diseases, in: The Role of Functional Food Security in Global Health, Elsevier, 2019, pp. 87–107.

[36] G.K. Fragiadakis, S.A. Smits, E.D. Sonnenburg, W. Van Treuren, G. Reid, R. Knight, et al., Links between environment, diet, and the hunter-gatherer microbiome, Gut Microb. 10 (2) (2019) 216–227.

[37] Y. Janssens, J. Nielandt, A. Bronselaer, N. Debunne, F. Verbeke, E. Wynendaele, et al., Disbiome database: linking the microbiome to disease, BMC Microbiol. 18 (1) (2018) 50.

[38] M.I. McBurney, C. Davis, C.M. Fraser, B.O. Schneeman, C. Huttenhower, K. Verbeke, et al., Establishing what constitutes a healthy human gut microbiome: state of the science, regulatory considerations, and future directions, J. Nutr. 149 (11) (2019) 1882–1895.

[39] L. Putignani, F. Del Chierico, A. Petrucca, P. Vernocchi, B. Dallapiccola, The human gut microbiota: a dynamic interplay with the host from birth to senescence settled during childhood, Pediatr. Res. 76 (1) (2014) 2–10.

[40] R.P. Dickson, J.R. Erb-Downward, F.J. Martinez, G.B. Huffnagle, The microbiome and the respiratory tract, Annu. Rev. Physiol. 78 (2016) 481–504.

[41] W.H. Man, W.A. de Steenhuijsen Piters, D. Bogaert, The microbiota of the respiratory tract: gatekeeper to respiratory health, Nat. Rev. Microbiol. 15 (5) (2017) 259.

[42] E.S. Charlson, J.M. Diamond, K. Bittinger, A.S. Fitzgerald, A. Yadav, A.R. Haas, et al., Lung-enriched organisms and aberrant bacterial and fungal respiratory microbiota after lung transplant, Am. J. Respir. Crit. Care Med. 186 (6) (2012) 536–545.

[43] E.S. Charlson, K. Bittinger, A.R. Haas, A.S. Fitzgerald, I. Frank, A. Yadav, et al., Topographical continuity of bacterial populations in the healthy human respiratory tract, Am. J. Respir. Crit. Care Med. 184 (8) (2011) 957–963.

[44] J.C. Madan, D.C. Koestler, B.A. Stanton, L. Davidson, L.A. Moulton, M.L. Housman, et al., Serial analysis of the gut and respiratory microbiome in cystic fibrosis in infancy: interaction between intestinal and respiratory tracts and impact of nutritional exposures, mBio 3 (4) (2012) e00251–12.

[45] A. Trompette, E.S. Gollwitzer, K. Yadava, A.K. Sichelstiel, N. Sprenger, C. Ngom-Bru, et al., Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis, Nat. Med. 20 (2) (2014) 159.

[46] C.M. Bassis, J.R. Erb-Downward, R.P. Dickson, C.M. Freeman, T.M. Schmidt, V.B. Young, et al., Analysis of the upper respiratory tract microbiotas as the source of the lung and gastric microbiotas in healthy individuals, mBio 6 (2) (2015) e00037–15.

[47] K.F. Budden, S.L. Gellatly, D.L. Wood, M.A. Cooper, M. Morrison, P. Hugenholtz, et al., Emerging pathogenic links between microbiota and the gut–lung axis, Nat. Rev. Microbiol. 15 (1) (2017) 55.

[48] T. Ichinohe, I.K. Pang, Y. Kumamoto, D.R. Peaper, J.H. Ho, T.S. Murray, et al., Microbiota regulates immune defense against respiratory tract influenza A virus infection, Proc. Natl. Acad. Sci. U.S.A 108 (13) (2011) 5354–5359.

[49] N. Lee, W.-U. Kim, Microbiota in T-cell homeostasis and inflammatory diseases, Exp. Mol. Med. 49 (5) (2017) e340.

[50] M. Salameh, Z. Burney, N. Mhaimeed, I. Laswi, N.A. Yousri, G. Bendriss, et al., The role of gut microbiota in atopic asthma and allergy, implications in the understanding of disease pathogenesis, Scand. J. Immunol. 91 (3) (2019) e12855.

[51] X. Du, J. Wei, D. Tian, M. Wu, C. Yan, P. Hu, et al., miR-182-5p contributes to intestinal injury in a murine model of *Staphylococcus aureus* pneumonia-induced sepsis via targeting surfactant protein D, J. Cell. Physiol. 235 (1) (2020) 563−572.

[52] X. Du, Q. Meng, A. Sharif, O.A. Abdel-Razek, L. Zhang, G. Wang, et al., Surfactant proteins SP-A and SP-D ameliorate pneumonia severity and intestinal injury in a murine model of *Staphylococcus aureus* pneumonia, Shock 46 (2) (2016) 164−172.

[53] D.N. O'Dwyer, R.P. Dickson, B.B. Moore, The lung microbiome, immunity, and the pathogenesis of chronic lung disease, J. Immunol. 196 (12) (2016) 4839−4847.

[54] H. Wang, P. Lian, X. Niu, L. Zhao, X. Mu, B. Feng, et al., TLR4 deficiency reduces pulmonary resistance to Streptococcus pneumoniae in gut microbiota-disrupted mice, PLoS One 13 (12) (2018) e0209183.

[55] A.K. Berger, B.A. Mainou, Interactions between enteric bacteria and eukaryotic viruses impact the outcome of infection, Viruses 10 (1) (2018) 19.

[56] S. Hanada, M. Pirzadeh, K.Y. Carver, J.C. Deng, Respiratory viral infection-induced Microbiome alterations and secondary bacterial pneumonia, Front. Immunol. 9 (2018) 2640.

[57] N. Li, W.-T. Ma, M. Pang, Q.-L. Fan, J.-L. Hua, The commensal microbiota and viral infection: a comprehensive review, Front. Immunol. 10 (2019) 1551.

[58] M.H. Grayson, L.E. Camarda, S.-R.A. Hussain, S.J. Zemple, M. Hayward, V. Lam, et al., Intestinal microbiota disruption reduces regulatory T cells and increases respiratory viral infection mortality through increased IFNγ production, Front. Immunol. 9 (2018) 1587.

[59] H.T. Groves, L. Cuthbertson, P. James, M.F. Moffatt, M.J. Cox, J.S. Tregoning, Respiratory disease following viral lung infection alters the murine gut microbiota, Front. Immunol. 9 (2018) 182.

[60] K. Xu, H. Cai, Y. Shen, Q. Ni, Y. Chen, S. Hu, et al., Management of corona virus disease-19 (COVID-19): the Zhejiang experience, J. Zhejiang Univ. Med. Sci. 49 (1) (2020) 147−157.

[61] L. Yu, Y. Tong, G. Shen, A. Fu, Y. Lai, X. Zhou, et al., Immunodepletion with Hypoxemia: A Potential High Risk Subtype of Coronavirus Disease 2019, medRxiv, 2020.

[62] S.J. Gabryszewski, O. Bachar, K.D. Dyer, C.M. Percopo, K.E. Killoran, J.B. Domachowske, et al., Lactobacillus-mediated priming of the respiratory mucosa protects against lethal pneumovirus infection, J. Immunol. 186 (2) (2011) 1151−1161.

[63] C. Qin, L. Zhou, Z. Hu, S. Zhang, S. Yang, Y. Tao, et al., Dysregulation of immune response in patients with COVID-19 in Wuhan, China, Clin. Infect. Dis. 71 (15) (2020) 762−768.

[64] K. Lange, M. Buerger, A. Stallmach, T. Bruns, Effects of antibiotics on gut microbiota, Dig. Dis. 34 (3) (2016) 260−268.

[65] M.T. Talley Andrews, D.I. Buckley, C. Heneghan, R. Deyo, N. Redmond, P.J. Lucas, et al., Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis, PLoS One 7 (1) (2012) e30334.

[66] WHO, London, Ontario, Canada, WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food, Vol. 30, 2002.

[67] H. Szajewska, Z. Konarska, M. Kolodziej, Probiotic bacterial and fungal strains: claims with evidence, Dig. Dis. 34 (3) (2016) 251−259.

[68] F. Guarner, A.G. Khan, J. Garisch, R. Eliakim, A. Gangl, A. Thomson, et al., World gastroenterology organisation global guidelines: probiotics and prebiotics October 2011, J. Clin. Gastroenterol. 46 (6) (2012) 468−481.

[69] A. Schreck Bird, P.J. Gregory, M.A. Jalloh, Z. Risoldi Cochrane, D.J. Hein, Probiotics for the treatment of infantile colic: a systematic review, J. Pharm. Pract. 30 (3) (2017) 366–374.

[70] M.E. Sanders, F. Guarner, R. Guerrant, P.R. Holt, E.M. Quigley, R.B. Sartor, et al., An update on the use and investigation of probiotics in health and disease, Gut 62 (5) (2013) 787–796.

[71] L. Hickey, S.E. Jacobs, S.M. Garland, P.S. Group, Probiotics in neonatology, J. Paediatr. Child Health 48 (9) (2012) 777–783.

[72] S. Ahrne, M.-L. Johansson Hagslatt, Effect of lactobacilli on paracellular permeability in the gut, Nutrients 3 (1) (2011) 104–117.

[73] M.B. De Morais, C.M.A. Jacob, The role of probiotics and prebiotics in pediatric practice, J. Pediatr. (Rio. J.) 82 (5 Suppl) (2006) S189–S197.

[74] C.N. Jacobsen, V.R. Nielsen, A.E. Hayford, P.L. Møller, K.F. Michaelsen, A. Paerregaard, et al., Screening of probiotic activities of forty-seven strains of *Lactobacillus* spp. by in vitro techniques and evaluation of the colonization ability of five selected strains in humans, Appl. Environ. Microbiol. 65 (11) (1999) 4949–4956.

[75] C. Hidalgo-Cantabrana, B. Sánchez, C. Milani, M. Ventura, A. Margolles, P. Ruas-Madiedo, Genomic overview and biological functions of exopolysaccharide biosynthesis in *Bifidobacterium* spp, Appl. Environ. Microbiol. 80 (1) (2014) 9–18.

[76] S. Oliva, G. Di Nardo, F. Ferrari, S. Mallardo, P. Rossi, G. Patrizi, et al., Randomised clinical trial: the effectiveness of *Lactobacillus reuteri* ATCC 55730 rectal enema in children with active distal ulcerative colitis, Aliment. Pharmacol. Ther. 35 (3) (2012) 327–334.

[77] L.J. Fooks, G.R. Gibson, Probiotics as modulators of the gut flora, Br. J. Nutr. 88 (S1) (2002) s39–s49.

[78] Y. Wang, X. Li, T. Ge, Y. Xiao, Y. Liao, Y. Cui, et al., Probiotics for prevention and treatment of respiratory tract infections in children: a systematic review and meta-analysis of randomized controlled trials, Medicine (Baltim.) 95 (31) (2016).

[79] H.M. Timmerman, C.J.M. Koning, L. Mulder, F.M. Rombouts, A.C. Beynen, Monostrain, multistrain and multispecies probiotics—a comparison of functionality and efficacy, Int. J. Food Microbiol. 96 (3) (2004) 219–233.

[80] S. Khanna, Microbiota replacement therapies: innovation in gastrointestinal care, Clin. Pharmacol. Ther. 103 (1) (2018) 102–111.

[81] S.M. Vindigni, C.M. Surawicz, Fecal microbiota transplantation, Gastroenterol. Clin. 46 (1) (2017) 171–185.

[82] H. Zhang, C. Yeh, Z. Jin, L. Ding, B.Y. Liu, L. Zhang, et al., Prospective study of probiotic supplementation results in immune stimulation and improvement of upper respiratory infection rate, Synth. Syst. Biotechnol. 3 (2) (2018) 113–120.

[83] A.T. Vieira, V.M. Rocha, L. Tavares, C.C. Garcia, M.M. Teixeira, S.C. Oliveira, et al., Control of *Klebsiella pneumoniae* pulmonary infection and immunomodulation by oral treatment with the commensal probiotic *Bifidobacterium longum* 51A, Microb. Infect. 18 (3) (2016) 180–189.

[84] A.S.Y. Lau, A Randomized, Double Blind, Placebo-Controlled Study on the Efficacy of *Bifidobacterium longum* Bb536 in Reducing Symptoms of Respiratory and Gastrointestinal Diseases Among Young Children [PhD Thesis], Universiti Sains Malaysia, 2018.

[85] C.K. Chan, J. Tao, O.S. Chan, H.-B. Li, H. Pang, Preventing respiratory tract infections by synbiotic interventions: a systematic review and meta-analysis of randomized controlled trials, Adv. Nutr. 11 (4) (2020) 979–988.

[86] T.L.A. Nguyen, S. Vieira-Silva, A. Liston, J. Raes, How informative is the mouse for human gut microbiota research? Dis. Model Mech. 8 (1) (2015) 1–16.

[87] N. Belkacem, N. Serafini, R. Wheeler, M. Derrien, L. Boucinha, A. Couesnon, et al., *Lactobacillus paracasei* feeding improves immune control of influenza infection in mice, PLoS One 12 (9) (2017) e0184976.

[88] L.M. Cox, S. Yamanishi, J. Sohn, A.V. Alekseyenko, J.M. Leung, I. Cho, et al., Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences, Cell 158 (4) (2014) 705–721.

[89] J.W. Mak, F.K. Chan, S.C. Ng, Probiotics and COVID-19: one size does not fit all, Lancet Gastroenterol. Hepatol. 5 (7) (2020) 644–645.

[90] L.E. Morrow, M.H. Kollef, T.B. Casale, Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial, Am. J. Respir. Crit. Care Med. 182 (8) (2010) 1058–1064.

[91] G. Jindal, R.K. Pandey, J. Agarwal, M. Singh, A comparative evaluation of probiotics on salivary mutans streptococci counts in Indian children, Eur. Arch. Paediatr. Dent. 12 (4) (2011) 211–215.

[92] J.H. Meurman, I. Stamatova, Probiotics: contributions to oral health, Oral Dis. 13 (5) (2007) 443–451.

[93] M.D. Williams, C.Y. Ha, M.A. Ciorba, Probiotics as therapy in gastroenterology: a study of physician opinions and recommendations, J. Clin. Gastroenterol. 44 (9) (2010) 631.

[94] P.D. Marsh, Dental plaque as a biofilm and a microbial community–implications for health and disease, in: BMC Oral Health, BioMed Central, 2006, p. S14.

[95] P.D. Marsh, Microbial ecology of dental plaque and its significance in health and disease, Adv. Dent. Res. 8 (2) (1994) 263–271.

[96] S.M.F. Ali, F. Tanwir, Oral microbial habitat a dynamic entity, J. Oral Biol. Craniofac. Res. 2 (3) (2012) 181–187.

[97] S. Piwat, B. Sophatha, R. Teanpaisan, An assessment of adhesion, aggregation and surface charges of Lactobacillus strains derived from the human oral cavity, Lett. Appl. Microbiol. 61 (1) (2015) 98–105.

[98] D.A. Devine, P.D. Marsh, J. Meade, Modulation of host responses by oral commensal bacteria, J. Oral Microbiol. 7 (1) (2015) 26941.

[99] S.J. Lewis, A.R. Freedman, The use of biotherapeutic agents in the prevention and treatment of gastrointestinal disease, Aliment. Pharmacol. Ther. 12 (9) (1998) 807–822.

[100] S. Twetman, Are we ready for caries prevention through bacteriotherapy? Braz. Oral Res. 26 (SPE1) (2012) 64–70.

[101] S. Twetman, M.K. Keller, Probiotics for caries prevention and control, Adv. Dent. Res. 24 (2) (2012) 98–102.

[102] A. Haukioja, E. Söderling, J. Tenovuo, Acid production from sugars and sugar alcohols by probiotic lactobacilli and bifidobacteria in vitro, Caries Res. 42 (6) (2008) 449–453.

[103] E. Isolauri, Y. Sütas, P. Kankaanpää, H. Arvilommi, S. Salminen, Probiotics: effects on immunity, Am. J. Clin. Nutr. 73 (2) (2001) 444s–450s.

[104] K. Saraf, M.C. Shashikanth, T. Priy, N. Sultana, N.C. Chaitanya, Probiotics-do they have a role in medicine and dentistry, JAPI 58 (2010) 488–492.

[105] B.S. Sivamaruthi, P. Kesika, C. Chaiyasut, A review of the role of probiotic supplementation in dental caries, Probiotics Antimicrob. Proteins 12 (4) (2020) 1300–1309.

[106] A.J. Ahola, H. Yli-Knuuttila, T. Suomalainen, T. Poussa, A. Ahlström, J.H. Meurman, et al., Short-term consumption of probiotic-containing cheese and its effect on dental caries risk factors, Arch. Oral Biol. 47 (11) (2002) 799–804.

[107] E. Caglar, S. Kavaloglu Cildir, S. Ergeneli, N. Sandalli, S. Twetman, Salivary mutans streptococci and lactobacilli levels after ingestion of the probiotic bacterium *Lactobacillus reuteri* ATCC 55730 by straws or tablets, Acta Odontol. Scand. 64 (5) (2006) 314–318.

[108] L. Näse, K. Hatakka, E. Savilahti, M. Saxelin, A. Pönkä, T. Poussa, et al., Effect of long–term consumption of a probiotic bacterium, *Lactobacillus rhamnosus* GG, in milk on dental caries and caries risk in children, Caries Res. 35 (6) (2001) 412–420.

[109] D. Gruner, S. Paris, F. Schwendicke, Probiotics for managing caries and periodontitis: systematic review and meta-analysis, J. Dent. 48 (2016) 16–25.

[110] R.G. Manjunath, Benefits of live microorganisms (Probiotics) in periodontal health, Int. J. Contemp. Dent. 2 (2011) 97–100.

[111] R. Chopra, S. Mathur, Probiotics in dentistry: a boon or sham, Dent. Res. J. 10 (3) (2013) 302.

[112] K. Noordin, S. Kamin, The Effect of probiotic mouthrinse on plaque and gingival inflammation, Ann. Dent. Univ. Malaya. 14 (1) (2007) 19–25.

[113] P.M. Harini, R.T. Anegundi, Efficacy of a probiotic and chlorhexidine mouth rinses: a short-term clinical study, J. Indian Soc. Pedod. Prev. Dent. 28 (3) (2010) 179.

[114] H. Shimauchi, G. Mayanagi, S. Nakaya, M. Minamibuchi, Y. Ito, K. Yamaki, et al., Improvement of periodontal condition by probiotics with *Lactobacillus salivarius* WB21: a randomized, double-blind, placebo-controlled study, J. Clin. Periodontol. 35 (10) (2008) 897–905.

[115] P.K. Thakkar, M. Imranulla, P.N. Kumar, G.M. Prashant, B. Sakeenabi, V.H. Sushanth, Effect of probiotic mouthrinse on dental plaque accumulation: a randomized controlled trial, Dent. Med. Res. 1 (1) (2013) 7.

[116] M.-S. Kang, B.-G. Kim, J. Chung, H.-C. Lee, J.-S. Oh, Inhibitory effect of *Weissella cibaria* isolates on the production of volatile sulphur compounds, J. Clin. Periodontol. 33 (3) (2006) 226–232.

[117] J.P. Burton, C.N. Chilcott, C.J. Moore, G. Speiser, J.R. Tagg, A preliminary study of the effect of probiotic *Streptococcus salivarius* K12 on oral malodour parameters, J. Appl. Microbiol. 100 (4) (2006) 754–764.

[118] E. Bouza, A. Burillo, Advances in the prevention and management of ventilator-associated pneumonia, Curr. Opin. Infect. Dis. 22 (4) (2009) 345–351.

[119] L. Lorente, S. Blot, J. Rello, Evidence on measures for the prevention of ventilator-associated pneumonia, Eur. Respir. J. 30 (6) (2007) 1193–1207.

[120] J.-L. Vincent, D. de Souza Barros, S. Cianferoni, Diagnosis, management and prevention of ventilator-associated pneumonia, Drugs 70 (15) (2010) 1927–1944.

[121] D.C. Bergmans, M.J. Bonten, C.A. Gaillard, J.C. Paling, S. van der GEEST, F.H. van TIEL, et al., Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study, Am. J. Respir. Crit. Care Med. 164 (3) (2001) 382–388.

[122] F. Hua, H. Xie, H.V. Worthington, S. Furness, Q. Zhang, C. Li, Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia, Cochrane Database Syst. Rev. 10 (10) (2016) CD008367.

[123] M. Koeman, A.J. van der Ven, E. Hak, H.C. Joore, K. Kaasjager, A.G. de Smet, et al., Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia, Am. J. Respir. Crit. Care Med. 173 (12) (2006) 1348–1355.

[124] A. Veitz-Keenan, D.M. Ferraiolo, Oral care with chlorhexidine seems effective for reducing the incidence of ventilator-associated pneumonia, Evid. Base Dent. 18 (4) (2017) 113–114.

[125] M.S. Opstrup, J.D. Johansen, L.H. Garvey, Chlorhexidine allergy: sources of exposure in the healthcare setting, Br. J. Anaesth. 114 (4) (2015) 704–705.

[126] M.N. Pemberton, J. Gibson, Chlorhexidine and hypersensitivity reactions in dentistry, Br. Dent. J. 213 (11) (2012) 547.

[127] G. Sharp, S. Green, M. Rose, Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature, ANZ J. Surg. 86 (4) (2016) 237–243.

[128] L.E. Morrow, M.H. Kollef, J.B. Bowers, T.B. Casale, Probiotic manipulation of the native flora in critically ill patients: an opportunity for ventilator-associated pneumonia prophylaxis? Chest 128 (4) (2005) 144S.

[129] D. Barraud, P.-E. Bollaert, S. Gibot, Impact of the administration of probiotics on mortality in critically ill adult patients: a meta-analysis of randomized controlled trials, Chest 143 (3) (2013) 646–655.

[130] L. Bo, J. Li, T. Tao, Y. Bai, X. Ye, R.S. Hotchkiss, et al., Probiotics for preventing ventilator-associated pneumonia, Cochrane Database Syst. Rev. 10 (2014).

[131] B. Klarin, G. Molin, B. Jeppsson, A. Larsson, Use of the probiotic *Lactobacillus plantarum* 299 to reduce pathogenic bacteria in the oropharynx of intubated patients: a randomised controlled open pilot study, Crit. Care 12 (6) (2008) R136.

[132] K. Liu, Y. Zhu, J. Zhang, L. Tao, J.-W. Lee, X. Wang, et al., Probiotics' effects on the incidence of nosocomial pneumonia in critically ill patients: a systematic review and meta-analysis, Crit. Care 16 (3) (2012) R109.

[133] W. Manzanares, M. Lemieux, P.L. Langlois, P.E. Wischmeyer, Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis, Crit. Care 20 (1) (2016) 262.

[134] G.J. Oudhuis, D.C. Bergmans, T. Dormans, J.-H. Zwaveling, A. Kessels, M.H. Prins, et al., Probiotics versus antibiotic decontamination of the digestive tract: infection and mortality, Intensive Care Med. 37 (1) (2011) 110–117.

[135] B. Klarin, A. Adolfsson, A. Torstensson, A. Larsson, Can probiotics be an alternative to chlorhexidine for oral care in the mechanically ventilated patient? A multicentre, prospective, randomised controlled open trial, Crit. Care 22 (1) (2018) 272.

[136] C.F. Linssen, O. Bekers, M. Drent, J.A. Jacobs, C-reactive protein and procalcitonin concentrations in bronchoalveolar lavage fluid as a predictor of ventilator-associated pneumonia, Ann. Clin. Biochem. 45 (3) (2008) 293–298.

[137] J. Wang, K. Liu, F. Ariani, L. Tao, J. Zhang, J.-M. Qu, Probiotics for preventing ventilator-associated pneumonia: a systematic review and meta-analysis of high-quality randomized controlled trials, PLoS One 8 (12) (2013) e83934.

[138] C. Alberda, L. Gramlich, J. Meddings, C. Field, L. McCargar, D. Kutsogiannis, et al., Effects of probiotic therapy in critically ill patients: a randomized, double-blind, placebo-controlled trial, Am. J. Clin. Nutr. 85 (3) (2007) 816–823.

[139] P. Forsythe, Probiotics and lung diseases, Chest 139 (4) (2011) 901–908.

[140] K. Madsen, A. Cornish, P. Soper, C. McKaigney, H. Jijon, C. Yachimec, et al., Probiotic bacteria enhance murine and human intestinal epithelial barrier function, Gastroenterology 121 (3) (2001) 580–591.

[141] L.P. van Minnen, H.M. Timmerman, F. Lutgendorff, A. Verheem, W. Harmsen, S.R. Konstantinov, et al., Modification of intestinal flora with multispecies probiotics reduces bacterial translocation and improves clinical course in a rat model of acute pancreatitis, Surgery 141 (4) (2007) 470–480.

[142] W.A. Walker, Mechanisms of action of probiotics, Clin. Infect. Dis. 46 (Suppl. 2) (2008) S87–S91.

[143] H.-J. Zhou, L. Yin, C.-Q. Chen, M.-M. Shi, M.-J. Zhang, Administration of probiotics reduces bacterial translocation after intestinal transplantation in rats, in: Transplantation Proceedings, Elsevier, 2010, pp. 4643–4647.

[144] D. Barraud, C. Blard, F. Hein, O. Marçon, A. Cravoisy, L. Nace, et al., Probiotics in the critically ill patient: a double blind, randomized, placebo-controlled trial, Intensive Care Med. 36 (9) (2010) 1540−1547.

[145] C. Forestier, D. Guelon, V. Cluytens, T. Gillart, J. Sirot, C. De Champs, Oral probiotic and prevention of *Pseudomonas aeruginosa* infections: a randomized, double-blind, placebo-controlled pilot study in intensive care unit patients, Crit. Care 12 (3) (2008) R69.

[146] Y. Fukushima, S. Miyaguchi, T. Yamano, T. Kaburagi, H. Iino, K. Ushida, et al., Improvement of nutritional status and incidence of infection in hospitalised, enterally fed elderly by feeding of fermented milk containing probiotic *Lactobacillus johnsonii* La1 (NCC533), Br. J. Nutr. 98 (5) (2007) 969−977.

[147] Siempos II, T.K. Ntaidou, M.E. Falagas, Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials, Crit. Care Med. 38 (3) (2010) 954−962.