ECRONICON OPEN ACCESS

EC PAEDIATRICS
Review Article

Synbiotics in Control of Pertussis Infection

Stojkovic Andjelka*

Department of Pediatrics Faculty of Medical Sciences, University of Kragujevac, Serbia

***Corresponding Author**: Stojkovic Andjelka, Professor, Department of Pediatrics Faculty of Medical Sciences, University of Kragujevac, Serbia.

Received: February 12, 2020; **Published:** March 12, 2020

Abstract

The efficiently and effectively treatment of respiratory infection with *Bordetella pertussis* (BPer) depends on the cellular glucose metabolism (CGM) at the level of the respiratory epithelium and on the activity of the insulin-secreting pancreatic beta cells, which means that the "elective" drug/preparation must have the potential to control CGM. Until now, treatment of respiratory infection with BPer has been partially successful if treated with macrolide at the beginning of the infection but the subsequent course of treatment is symptomatic and insufficiently efficient and effective. The potential of individual probiotic bacteria and synbiotics in controlling CGM, enhancing the host immune response, local immunomodulation at the level of the respiratory epithelium and controlling opportunistic respiratory infection should be considered and clinically evaluated. Synbiotic stimulates enhanced secretion of immunoglobulins A and G which act by neutralizing the pertussis toxin and prevent infection of the epithelial cell and contribute to protection against BPer infection.

Keywords: *Pertussis; Child; Probiotics; Treatment*

Introduction

Pertussis or whooping cough is a highly contagious respiratory disease transmitted by polluted aerosol drops, which occupies an important place in the morbidity and mortality of young children (10th place globally) [1]. Pertussis is still an endemic disease in all countries of the world, although vaccination covers 86% of the world population after 3 doses of the pertussis vaccine (World Health Organization (WHO) 2014) [2]. According to the same data [2,3], the number of deaths is still high (in 2013, 63,000 children under 5, or 4% in the population of children under 1 and 1% in children 2 to 4).

The causes of pertussis and pertussis-like diseases are *Bordetella pertussis*, respiratory syncytial virus (RSV), parainfluenza virus and *Mycoplasma pneumonia* (My.pn). Natural *Bordetella pertussis* infection does not provide long-term protection against pertussis [4]. Today, we recognize 9 strains of the genus *Bordetella*, which are primarily opportunistic germs in humans and mammals (e.g., *B. pertussis*, *B. parapertussisHu*, *B. bronchiseptica*) [5].

Control of pertussis infection by vaccines

Transplancentric passage of antibodies to *B. pertussis* is low and insufficient to protect infants from the clinical manifestation of the disease, regardless of whether the mother has recently been vaccinated against pertussis. Prospectively the protection with transplacental transmitted antibodies to *B. pertussis* may have only the newborns. The infant's sensitivity to 6 months of age is extremely high, so the disease is clinically manifested as life-threatening, making it extremely important to start vaccination against pertussis from the 6th week of life, thereby achieving a protection level of 50% [2,3].

On average, acellular vaccines (aP) against pertussis are more effective than whole-cell vaccines (wP), but they are less effective than the most effective whole-cell vaccines [2,3]. The reason is that after vaccination with the aP vaccine, the protective effect is shorter and the effect on respiratory mucosa infection and infection transmission is limited. aP vaccines induce the production of antibodies that promote a Th2 dominant response and a weaker Th1 and Th17 response, whereas wP vaccines and natural infection of *B. pertussis* induce a Th1 and Th17 response. The cellular Th1 and Th17 mediated immune response are essential for clearance by *B. pertussis* and the effect of long-term protection while antibodies protect against disease [6]. The cell-dominant Th2 response provides weaker and shorter-term protection because aP contains fewer antigens (3 - 5 compared to > 3000 antigens in the wP vaccine), which results in suppression after epitope binding of the antigen such that children vaccinated with the aP vaccine exhibit increased sensitivity on *B. pertussis* throughout life.

What should be borne in mind is that the full protective effect of the pertussis vaccine is only achieved after 3 doses, starting from the 6th week of life (regardless of the type of vaccine administered), after that the protection against severe pertussis is incremental after each additional dose, and that the subsequent booster dose extends the protection period to 7 years (regardless of which vaccine is administered). Declining vaccine protection and diminished immunity by circulating *B. pertussis* increase adolescent and adult susceptibility, which is the reason for a persistent cough in them [7] and they become the source of *B. pertussis* transmission to unvaccinated young children (74% to 96%) [8]. Neither should be neglected the cyclical occurrence of *B. pertussis* in nature, which contributes to an increase in the rate of morbidity and mortality. The reasons for the recurrence of a high rate of pertussis disease in the high vaccination population in recent decades are the loss of the so-called "herd" immunity, suboptimal humoral response, increased levels of pertussis awareness and better recognition, better diagnosis and adaptation of the bacterium (changes in antigen profile and increased virulence, the emergence of a promoter of 3 alleles of circulating strain instead of ptxP2 and ptxP1 alleles) [9].

All of these reasons have contributed to the rise in pertussis disease in many countries around the world. It should be borne in mind that the increase in pertussis disease in some countries of the world is a complex problem and is not solely due to the use of aP instead of the wP vaccine. Therefore, WHO proposes epidemiological surveillance of pertussis [2,3], especially laboratory-confirmed disease (PCR technique), in low- and middle-income countries, especially in infants up to 6 months, with particular reference to hospitalized and fatal cases. At the same time, in the light of current knowledge about the immune potential of Bordetella pertussis, other treatment options for this infection should be considered, as well as other prevention options.

Our increased interest in pertussis is also due to pertussis complications four times more common in infants younger than 6 months, not considering if the complications are pulmonary (bronchopneumonia, pulmonary hypertension, respiratory arrest), neurological (encephalopathy), shock, cardiac arrest, nutritional complications or death. Complications occur in unvaccinated patients and/or if treatment is initiated just during the paroxysmal phase of pertussis. Macrolides can prevent or mitigate the clinical picture of pertussis if applied during the incubation period or early catarrhal stage [10]. If macrolide is administered during the paroxysmal phase of the disease, the clinical course of the disease is not altered, but only *B. pertussis* transmission is reduced, as the bacterium in the nasopharynx is eliminated.

Insight in pathogenesis and clinical features of pertussis infection

To prevent complications of pertussis and to shed light on other treatment and prevention options for pertussis, we need to look at current knowledge about the pathogenesis of pertussis. The pathogenesis of pertussis is not yet fully understood, although the activities of some parts of the small gram-negative coccobacillus are known. Filamentous hemagglutinin (FHA), pertactin (PRN) and fimbriae (FIM) are known to facilitate attachment of *B. pertussis* to host respiratory epithelial cells, while pertussis toxin (PT), tracheal cytotoxin (TCT) and adenylate cyclase toxin (ACT) contribute to dysfunction immune (defense) host factors and destruction of epithelial cells. *Bordetella* strains of bacteria, depending on environmental conditions, change their phenotypic state expressing the listed virulence factors (PT, FHA, PRN, FIM type 2 and type 3, ACT, TCT and lipooligosaccharide), which results in long-term survival in the respiratory epithelium.

The incubation period of pertussis is 9 to 10 days (range is 6 to 20 days) followed by a catarrhal phase with accompanying cough which is paroxysmal (cough attacks), hoarse (high-pitched, coarse, like dog barking, similar to donkey onomatopoeia), especially intense during the night, often accompanied by vomiting and low fever. In infants and young infants, apnea and cyanosis may be the first symptoms of pertussis. In adolescents and adults, the only clinical symptom of pertussis is usually a persistent cough without hoarseness. The convalescence of pertussis can last for months, and then the patient coughs persistently.

Following bacterial adherence to the ciliated epithelium in the nasopharynx and trachea, a local cellular immune response has been activated followed by increased mucociliary clearance, the release of antimicrobial peptides, and inflammatory cell activities. During the catarrhal phase, the symptoms are similar to those in the common cold and other upper respiratory tract infections. After 7 to 14 days, the disease progresses to a paroxysmal phase, which can last for 1 to 10 weeks and is characterized by a change in the period of normal airway function with periods of numerous, severe attacks of spasmodic cough followed by inspiratory hoarseness and frequent vomiting. The onset of activation of the humoral immune response coincides with the destruction of *B. pertussis* by local immune mechanisms, but the symptoms persist and progressively weaken for a month or more, which is referred to as the convalescent phase. In children under one year of age, a severe clinical picture is often present due to the dispersal of bacteria into the lungs, followed by necrotizing bronchiolitis, interalveolar hemorrhage, fibrinous pulmonary edema, pulmonary hypertension, respiratory failure, and death. A severe clinical picture of pertussis is accompanied by lymphocytosis.

The release of antimicrobial peptides at the level of the respiratory epithelium of the host is of limited capacity, which means that invasion of *B. pertussis* during the catarrhal phase of the disease (7 to 14 days) leads to the depletion of this defense mechanism, which causes a risk of *B. pertussis* survival in the respiratory epithelium and changes in its virulence, which results in the prolongation of the disease, especially the paroxysmal phase of the disease. Support for this defense mechanism in the respiratory epithelium can be provided by "good bacteria" or probiotic germs, especially when consumed with prebiotics in the form of synbiotics. Probiotic bacteria, via antigen-presenting cells in the gut, stimulate the maturation of T lymphocytes into T regulatory lymphocytes, which contribute to the establishment of local immune balance at the level of not only the intestinal but also the respiratory epithelium. UNICEF [11] is in the consensus that probiotics can help to achieve the balance of different types of bacteria in the body, which is essential for health. Here, we will focus our attention on the potential of probiotics or synbiotics (mixed of probiotic strains with prebiotic) in the treatment and prevention of pertussis. There are also numerous recommendations on the length of administration of probiotics or synbiotics to control respiratory infection and allergic inflammation. Our results, insights, and experiences will be presented here in comparison with others.

Control of pertussis infection with probiotics/synbiotic

Probiotic bacteria, independently or from synbiotics, participate in direct and indirect cross talks with dendritic cells in the gut epithelium, thus stimulating cellular immune responses and polarizing the humoral immune response [12]. During direct cross talks, dendritic cells receive information, not only from probiotic bacteria but also from commensal and pathogenic bacteria, so that different subpopulations of dendritic cells are differentiated. When there are enough probiotic bacteria at the level of the intestinal mucosa, they activate a higher number of dendritic cells than the number of dendritic cells activated by commensal and pathogenic bacteria. At the same time, indirect cross talks of probiotic bacteria with large intestinal mucosal epithelial cells release large quantities of thymus stromal lymphopoietin (TSLP), then probiotic bacteria stimulate ligand proliferation (necessary for the transfer of information between B and T lymphocytes) as well as interleukins-8 (IL8) and transforming growth factor-beta (TGF-beta). Complicated negotiations with T lymphocyte subpopulations continue. Increased production of TGF-beta (from dendritic cells activated by probiotic bacteria) will activate T-regulatory lymphocytes, which will continue production of TGF-beta and IL10, which now has a systemic effect in stimulating immature B lymphocytes to mature in mucosal lymphoid tissue (MALT in intestine, bronchi, nasopharynx, middle ear, genitourinary), which releases increased amount of total immunoglobulin A (IgA) as well as subclasses of IgA - secretory IgA that prevents penetration of the antigen

(*B. pertussis*). Increased activity in MALT is accompanied by stronger opsonization with the help of IgG and fibronectin, macrophages are activated along the entire bronchial tree and mostly in the alveoli, and vasoactive mediators and proinflammatory cytokines (IL12, IL18, interferon-gamma, tumor necrosis, factor-alpha, IL1) are released in increased amounts in the bronchial tree. Lactoferrin released is bacteriostatic, while lysozyme and interferon-gamma are bactericidal, and alpha-1-antitrypsin inhibits inflammatory enzymes and neutrophil migration.

Overall, an important effect of probiotic bacteria is achieved in terms of restoring the function of host immune (defense) factors, nullifying the effect of disease (pertussis toxin (PT) -mediated disease [13]), restoring respiratory epithelial cells, inhibiting the expression of *B. pertussis* virulence factors prevents the phenotypic alteration of strains of *B. pertussis* and its survival in the respiratory epithelium, and this in clinical terms means a shortening of the paroxysmal and convalescent phase of the disease, that is, faster healing from pertussis. From the perspective of a young infant who has not received 3 doses of pertussis vaccine, the use of probiotic bacteria may at least reduce the clinical picture of pertussis or even prevent a clinical development of a clinical picture of pertussis.

Probiotics stimulate the production of short-chain fatty acids, which causes a decrease in the pH of the medium in which the bacteriostatic effect increases. In the presence of probiotic bacteria, the production of anti-microbial peptides and mucins [14,15] exhibiting bactericidal activity and the production of reactive oxygen strains that raise oxidative stress for pathogens in the microenvironment is enhanced. Overall, micro-conditions are disturbed so that *B. pertussis* cannot survive but collapses and is prevented from attaching to the proximal portion of the ciliated respiratory epithelium. The increased amount of secretory IgA and lysozyme contributes to better mucociliary transport or optimal lung clearance index. Probiotic bacteria increase the capacity of the local immune defense mechanism to *B. pertussis* but do not increase the concentration of antibodies against *B. pertussis* toxins and pneumococci in healthy children, which was established after the simultaneous administration of probiotics (*Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* ssp. Lactis) and vaccine against *B. pertussis* [16]. There is still no research examining the effects of probiotic or synbiotic consumption during incubation, catarrhal phase, paroxysmal, and convalescent phase of pertussis, but studies have concluded that the use of probiotics or synbiotics contributes to reducing the incidence of respiratory infections in young children.

It has been proven [17] that during the synbiotic supplementation, not only IgA production but also IgG and IgM production in the reciprocal ratio of 10.9: 1.4: 1.9 increase, which means that stimulation and systemic immune response, which is involved in the fight against *B. pertussis*, is achieved and that there is not only the stimulation of the local respiratory epithelial defense mechanism. IgA and IgG may neutralize the pertussis toxin. *Lactobacillus acidophilus* Rosell52 stimulates macrophage activation, increase in tumor necrosis factor (TNF) -alpha production, increase in immune cell count, B-lymphocyte activation and IgM antibody increase, while *Bifidobacterium bifidum* Rosell71 stimulates T-helper lymphocyte growth, inhibits IL8 and IL10 production, stimulates IL8 and IL10 production, stimulates tolerance and improves blood lipid ratio, which overall contributes to a better immune defense response and better nutritional status. *Bifidobacterium infantis* Rosell33 has a similar effect. During synbiotic supplementation, the release of an increased amount of IgA occurs over 8 weeks [17]. At the same time, the probiotic effect was accompanied by a decrease in IgE production, suggesting that atopic children could achieve immune Th1/Th2 balance, immunosuppression, and immunotolerance against potential allergens. This means that probiotic supplementation can facilitate and accelerate the cure of pertussis respiratory infection while controlling the risk of an adverse allergic response [17]. In the study [17], the respiratory infections drop from 62.7% to 7.8% during the 3 months of synbiotic consumption was determined. Prolonged and continuous administration of synbiotic continues the aforementioned production of major classes of immunoglobulins, which is maximal after 9 months of administration since it takes so long to reach the “full pool” of graduated B-lymphocytes, regulatory T-lymphocytes and tolerogenic dendritic cells [17], which reduces the incidence of wheezing in atopic children.

Conclusion

Based on current knowledge about the desired and undesired effects of probiotics or synbiotic in the control of respiratory infections, including pertussis, we can conclude that the effects are achievable, but it is not clear to what extent. It has not yet been determined which

probiotic strains could provide the most effective protective effect against *B. pertussis*, whether it is sufficient to start probiotic bacterial supplementation in the catarrhal phase of the disease or not, or should new routine diagnostic options be found for pertussis infection during the incubation period in order to start supplementation with probiotics or synbiotic? Would the use of synbiotic be more appropriate or the use of a unique probiotic strain (and which one) is sufficient? We are going to have answers to a number of these questions in the future, and now the important option for us is the early application of probiotics from birth, as well as vaccination (better aP than wP). Until a better vaccine or better way to protect against pertussis is discovered, it is important for us to achieve the following goals in terms of alleviating the clinical picture of pertussis or even to prevent the development of a clinical picture of pertussis in a young infant who has not received 3 doses of the pertussis vaccine, or to shorten the paroxysmal and convalescent phase of the disease in order to cure the disease faster supplementing probiotic bacteria from birth.

Conflict of Interest

I declare any conflict of interest.

Bibliography

1. Tan T., *et al*. "Pertussis Across the Globe: Recent Epidemiologic Trends From 2000 to 2013". *Pediatric Infectious Disease Journal* 34.9 (2015): e222-232.
2. "Pertussis vaccines: WHO position paper - 28 August 2015". *Weekly Epidemiological Record* 35.90 (2015): 433-460.
3. "Meeting of the Strategic Advisory Group of Experts on immunization, April 2014 - conclusions and recommendations". *Weekly Epidemiological Record* 89.21 (2014): 221-236.
4. Amirthalingam G., *et al*. "Effectiveness of maternal pertussis vaccination in England: an observational study". *Lancet* 384.9953 (2014): 1521-1528.
5. Melvin JA., *et al*. "*Bordetella pertussis* pathogenesis: current and future challenges". *Nature Reviews Microbiology* 12.4 (2014): 274-288.
6. Kapil P and Merkel TJ. "Pertussis vaccines and protective immunity". *Current Opinion in Immunology* 59 (2019): 72-78.
7. Wright SW., *et al*. "Pertussis infection in adults with persistent cough". *Journal of the American Medical Association* 273.13 (1995): 1044-1046.
8. Wiley KE., *et al*. "Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy". *Vaccine* 31.4 (2013): 618-625.
9. Hovingh Elise Sofie. "Unraveling the interactions between *Bordetella pertussis* and the innate immune system" (2018).
10. Tiwari T., *et al*. "Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines". *Morbidity and Mortality Weekly Report. Recommendations and Reports* 54.RR-14) (2005): 1-16.
11. Children, food and nutrition. Growing well in a changing world. The state of the world's children 2019. United nations children's fund (UNICEF) (2019): 100.
12. Levy M., *et al*. "Dysbiosis and the immune system". *Nature Reviews Immunology* 17.4 (2017): 219-232.
13. Cherry JD. "The 112-Year Odyssey of Pertussis and Pertussis Vaccines-Mistakes Made and Implications for the Future". *Journal of the Pediatric Infectious Diseases Society* 8.4 (2019): 334-341.

14. Isolauri E., *et al*. "Improved immunogenicity of oral D x RRV reassortant rotavirus vaccine by *Lactobacillus casei* GG". *Vaccine* 13.3 (1995): 310-312.

15. Paineau D., *et al*. "Effects of seven potential probiotic strains on specific immune responses in healthy adults: a double-blind, randomized, controlled trial". *FEMS Immunology and Medical Microbiology* 53.1 (2008): 107-113.

16. Sørensen AC., *et al*. "Probiotics and the immunological response to infant vaccinations; a double-blind randomized controlled trial". *Clinical Microbiology and Infection* 25.4 (2019): 511.e1-511.e7.

17. Stojkovic A., *et al*. "Clinical trial/experimental study (consort compliant): Optimal time period to achieve the effects on synbiotic-controlled wheezing and respiratory infections in young children". *Srpski Arhiv za Celokupno Lekarstvo* 144.1-2 (2016): 38-45.

Volume 9 Issue 4 April 2020