



# Impact of Breast Milk Secretory Immunoglobulin A on Infants Acute Gastroenteritis

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## Abstract

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**BACKGROUND:** Acute gastroenteritis is one of the most common infections in childhood and it can be especially dangerous in the first 6 months of life with a higher risk of moderate and severe dehydration, especially in infants who are not exclusively breastfed. Secretory immunoglobulin A (sIgA) is the first line of defense on the intestinal epithelium from pathogenic microorganisms and intestinal toxins.

**AIM:** The aim of this study was to determine whether breast milk sIgA has some protective effect on the intestinal epithelium as well as on the severity and duration of the clinical signs in infants with acute gastroenteritis depending on the type of nutrition.

**MATERIALS AND METHODS:** A total of 23 infants with acute gastroenteritis divided into two groups based on the feeding patterns (type of milk) were included in the study. Investigated indicators were severity of symptoms, dehydration degree, and the need for parenteral rehydration.

**RESULTS:** We identified a statistically significant association between group affiliation and the sIgA levels in stool between the first and the second groups ( $p = 0.001346$ ). The most common cause of acute gastroenteritis in infants was *Rotavirus*. Our study has shown that exclusive breastfeeding reduces the risk of *Rotavirus* infection, especially in the first 6 months of life, OR = 0.0758, 95% confidence interval (CI) (0.0071–0.8074).

**CONCLUSION:** The presence of breast milk sIgA in infants has an effect on the severity of the clinical picture of acute gastroenteritis by reducing the frequency of vomiting, the number and severity of diarrheal episodes, the risk of moderate and severe dehydration, and fever frequency.

## Introduction

Acute gastroenteritis is one of the most common infections in childhood and it can be especially dangerous in the first 6 months of life with a higher risk of increased water and electrolyte loss with consequent moderate to severe dehydration, especially in infants who are not exclusively breastfed. The incidence of acute gastroenteritis ranges from 0.5 to 2 episodes per child per year in children younger than 3 years. At this age, acute gastroenteritis is the most common cause of hospitalization [1]. Acute gastroenteritis is defined as a decrease in stool consistency and/or an increase in the frequency of discharges ( $\geq 3$  in 24 h) with or without fever and vomiting [1]. *Rotavirus* is the most common cause of acute gastroenteritis, rarer causes are *Adenovirus*, *Norovirus*, and *Astrovirus*. Bacterial pathogens include *Salmonella*, *Shigella*, and less commonly *Escherichia coli*, *Campylobacter jejuni*, and *Yersinia enterocolitica*. Enterocyte infection leads to cell death, lumen extrusion, and atrophy of the intestinal villi, resulting in reduced intestinal surface area, with impaired digestive and absorption functions and acute transient malabsorptive diarrhea.

The secretory immunoglobulin A (sIgA) is the first line of defense for the intestinal epithelium from

pathogenic microorganisms and intestinal toxins. It prevents the binding of microorganisms to epithelial receptors by binding it to the Fc receptor on the surface of the pathogen, trapping microorganisms in the mucus, and enabling their removal by stimulating peristalsis and mucociliary activity [2], [3]. sIgA is able to directly reduce bacterial virulence and it has an effect on the composition of the intestinal microflora [2]. IgA is a weak activator of complement and it poorly opsonizes [2].

Breast milk is a link between the mother's immune system and the infant. Although infants have antibodies vertically transmitted from the mother (transplacental), they remain unprotected when they come in contact with new microorganisms [4]. sIgA is the most important immunoglobulin in breast milk not only because of its high concentration but also because of its biological activity [5], [6]. Natural and specific sIgA antibodies in breast milk are capable of binding to commensal bacteria and may be involved in establishing of the intestinal microflora of the newborn, which, in turn, stimulates the maturation of intestinal lymphatic tissue, resulting in the production of sIgA with limited affinity of recognition and removal of pathogenic microorganisms [2]. A number of studies have confirmed that exclusive breastfeeding has a protective role and

reduces the risk of diarrhea, especially in infants up to 6 months of age [7], [8].

The aim of this study was to assess whether sIgA from breast milk has a protective effect on the intestinal epithelium by evaluating the severity and duration of the clinical signs in infants under 6 months with acute gastroenteritis depending on the type of nutrition.

## Materials and Methods

### Study design

This was a prospective cohort study started on November 15, 2018, and lasted until December 31, 2019. The study included newborns and infants from birth to 6 months of age who were diagnosed with acute gastroenteritis. All infants were hospitalized at the Children's Department in Clinical Hospital – Shtip. Parents' written consent was obtained for each infant included in the study after extensive communication with them. An appropriate survey questionnaire was designed and responses were obtained from the infants' mothers. The questionnaire covered the following segments: Infant age, nutrition (breast milk, milk formula, or cow's milk), and weaning practice. Information on the onset of symptoms of acute gastroenteritis in the past 24 h before admission, as well as information on the diet and health status of the nursing mother were included. Infants were divided into two groups according to age in months and according to milk nutrition and introduction of complementary food.

Group I included newborns and infants from birth to 6 months who were exclusively breastfed. Group II included newborns and infants from birth to 6 months of age who were not exclusively breastfed and were on mixed milk nutrition.

Exclusively breastfed were infants who were fed only with breast milk and did not receive additional food or fluids (excluding oral rehydration solution, vitamins, minerals, and medications). The clinical picture and degree of dehydration were determined by physical examination and the degree of dehydration was divided into mild, moderate, and severe through the use of a clinical scoring system. (World Health Organization: Integrated management of childhood illness-Module 4, Diarrhea). For each infant included in the study, a record sheet was filled and according to the severity of the clinical signs, the need for parenteral rehydration was assessed during the hospital stay. The study did not include infants whose diarrhea was due to a surgical or extra-intestinal cause, as well as infants who had received immunosuppressive therapy.

### Laboratory methods

From each infant included in the study, two samples of diaper stool were taken with a plastic spatula.

One sample stool was collected in a sterile plastic cup with the general data of the patient and the code written on it and within 30 min, it was taken to the Microbiological Laboratory in the Center for Public Health (CPH) – Shtip. In this stool sample, it was proved the presence of *Rotavirus* and *Adenovirus* with immunochromatographic test (DUO ROTA-ADENOVIRUS - Check-1 VEDA. LAB, Alencon-France). From the same stool sample, a coproculture was performed which disproved the presence of enteropathogenic bacteria by sowing the stool sample on a suitable substrate. The second stool was frozen at  $-80^{\circ}\text{C}$  and in that sample, the sIgA level was determined quantitatively by ELISA method with ELISA kit test by Immundiagnostik, Bensheim, Germany.

### Statistical analysis

The collected data were processed using the statistical program SPSS 20 and the following statistical methods: Attributive statistical series were analyzed by determining percentages. Numerical series were analyzed with central tendency measures and with data dispersion measures. Statistical significance of the probability between numerical series was determined using Student's t-test. The odds ratio-OR cross-correlation is used to determine the relationship between the dependent-criterion variable and the independent. With Shapiro-Wilk test, the normality of variable distribution was tested. For confidence interval (CI) (95% CI), statistical significance was defined at the level of standard error  $<0.05$  (p). The results are shown in tables and figures.

## Results

The analysis included 23 hospitalized infants from birth to 6 months of age with a diagnosis of acute gastroenteritis, divided into two groups. The first group included 7 (30.4%) infants and the second group included 16 (69.6%) infants, divided by age expressed in months and type of nutrition.

Table 1 presents the infants with acute gastroenteritis by gender and sex.

**Table 1: Distribution of the infants according to the gender and age**

Group	I		II	
	Number	%	Number	%
Gender				
Male	4	57.1	9	56.25
Female	3	42.9	7	43.75
Age in months	Number	Mean ! SD	Number	Mean ! SD
	7	2.1 ! 0.899735	16	3.4 ! 1.454877

SD: Standard deviation.

The average infant age in the first group was  $2.1 \pm 0.9$  months and in the second group was  $3.4 \pm 1.5$  months.

The distribution of the clinical signs in both groups is presented in Table 2, which included the average number of vomiting, average number of liquid

**Table 2: Clinical condition 24 h before admission and during the hospitalization**

Group	Average I	Average II	t-test	p	N I	N II	SD I	SD II
Number of vomiting 24 h before admission	0.285714	4.56250	-3.40460	0.002669	7	16	0.487950	3.265348
Number of stools 24 h before admission	3.7	10.4	-3.49610	0.002152	7	16	0.755929	4.951431
Number of stools during the hospitalization	9.0	21.2	-3.67211	0.001419	7	16	2.236068	8.549610
Number of vomiting during the hospitalization	0.3	3.0	-2.90250	0.008516	7	16	0.755929	2.394438
Number of parenteral rehydration days	0.7	2.0	-3.11436	0.005246	7	16	0.755929	0.966092
Number of hospitalization days	4.1	4.9	-1.02224	0.318302	7	16	1.573592	1.768945

SD: Standard deviation, N: Number.

stools, fever, degree of dehydration, number of days of parenteral rehydration, and length of hospital stay. The average number of vomiting 24 h before admission in infants in the first group was  $0.3 \pm 0.5$ , in the second group was  $4.6 \pm 3.3$ , the difference was statistically significant ( $p = 0.002669$ ). The average number of liquid stools in infants 24 h before admission in the first group was  $3.7 \pm 0.8$ , in the second group  $10.4 \pm 4.9$ , and the difference was statistically significant ( $p = 0.002152$ ). Fever was reported in 14.3% of infants in the first group and in 81.25% in the second group, with statistically significant percentage difference ( $p = 0.0025$ ). All infants from the first group had mild degree of dehydration, in the second group, a mild degree of dehydration was registered in 25.0%, moderate in 43.75%, and a severe degree of dehydration in 31.25% of infants. The average number of liquid stools during treatment in the first group was  $9.0 \pm 2.2$ , and in the second group was  $21.2 \pm 8.5$ , the difference between the average number of liquid stools was statistically significant ( $p = 0.001419$ ). The average number of vomiting during treatment in the first group was  $0.3 \pm 0.8$ , and in the second group was  $3.0 \pm 2.4$ , the difference between the average number of vomiting was statistically significant ( $p = 0.008516$ ). The average number of parenteral rehydration days in the first group was  $0.7 \pm 0.8$ , and in the second group, it was  $2.0 \pm 1.0$ , the difference between the average number of parenteral rehydration days was statistically significant ( $p = 0.005246$ ). The average number of hospital days (length of stay) in the first group was  $4.1 \pm 1.6$ , and in the second group, it was  $4.9 \pm 1.8$ , the difference between the average number of hospital days was statistically insignificant for  $p > 0.05$  ( $p = 0.318302$ ).

*Rotavirus* was positive in 12 stool samples. In the first group, *Rotavirus* was positive in 1 (14.3%) infant, and in the second group, *Rotavirus* was positive in 11 (68.75%) infants. One infant from the second group was isolated *Shigella flexneri* and in one infant from the same group was isolated *Adenovirus* (Figure 1).

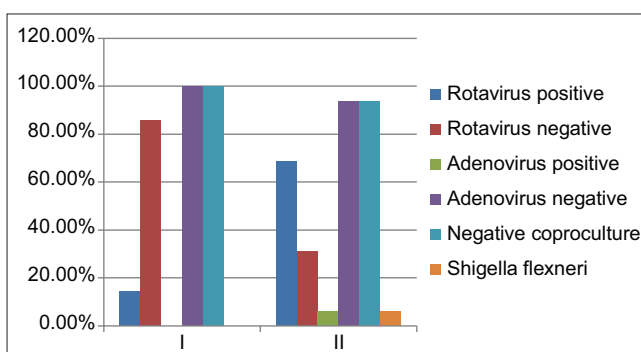


Figure 1: Microbiological findings in stool

The mean value of sIgA in infants diagnosed with acute gastroenteritis in the first group was  $3902.6 \pm 1496.8 \mu\text{g/ml}$ , and in the second group, it was  $531.9 \pm 506.2 \mu\text{g/ml}$ , the difference between the mean values was statistically significant for  $p < 0.05$  ( $p = 0.000000$ ) (Figure 2).

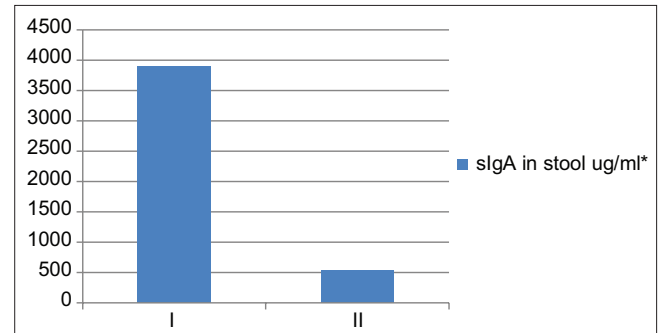
Figure 2: Average value of sIgA in infants with acute gastroenteritis. sIgA: Secretory immunoglobulin A. t-test = 8.198331;  $p = 0.000000$  (statistically significant)

Table 3 shows the effect of sIgA on the degree of dehydration, vomiting symptom, and fever in infants with acute gastroenteritis. We found a statistically significant association between dehydration rate, vomiting frequency, and fever between the first and second groups. Infants who were sIgA positive had a significantly lower degree of dehydration, lower vomiting frequency, and fever.

**Table 3: Effect of sIgA on the clinical condition in infants with acute gastroenteritis**

	Negative sIgA N=12	Positive sIgA N=11	p
Dehydration degree (%)			$p=0.004708$
Mild	2 (16.6)	9 (81.8)	
Moderate	5 (41.7)	2 (18.2)	
Severe	5 (41.7)	0	
Fever (%)			$p=0.036074$
No	2 (16.7)	7 (63.6)	
Yes	10 (83.3)	4 (36.4)	
Vomiting (%)			$p=0.000383$
No	1 (8.3)	9 (75.0)	
Yes	11 (91.7)	2 (25.0)	

N: Number, sIgA: Secretory immunoglobulin A.

A statistically significant association between exclusive breastfeeding and *Rotavirus* was registered for  $p < 0.05$  ( $p = 0.016128$ ). Exclusive breastfeeding is effective in preventing *Rotavirus* infection by reducing the risk of *Rotavirus* infection in infants, especially in the first 6 months of life, OR = 0.0758, 95% CI (0.0071–0.8074).

## Discussion

Several studies have confirmed that breastfed infants have significantly higher concentrations of sIgA

in the stool than those who have been formula fed, concluding that breast milk provides large amounts of sIgA for infants and plays a major role in protection and promotion of the immune function of the infant's digestive tract [9], [10], [11], [12], [13]. The results of sIgA in stool in infants with acute gastroenteritis from our research correlate with the results of the above studies. We observed a statistically significant association between group affiliation and the sIgA levels in stool between the first and the second groups. Numerous studies have shown that sIgA from breast milk has a protective effect against diarrhea in the first 6 months of life. Dialo *et al.*, 2019 [14], noticed that breastfeeding discontinuation before the 3<sup>rd</sup> month was found to be significantly associated with a high incidence of diarrhea at 6 months of age and between 6 and 12 months. Breastfeeding discontinuation (weaning) before the 6<sup>th</sup> month was also associated with a higher incidence of diarrhea at 6 months of age. Infants who were on milk formula for  $\geq 3$  months had a higher incidence of diarrhea between 6 and 12 months. Krawczyk *et al.*, 2016 [15], and Plenge-Bönig *et al.*, 2010 [16], have found that exclusive breastfeeding is effective in preventing *Rotavirus* infection by reducing the risk of *Rotavirus* infection in children, especially in the first 6 months of life. A few studies have shown that *Rotavirus* is a more common cause of acute gastroenteritis in infants than *Adenovirus* [17], [18]. These results support our findings that the most common cause of acute gastroenteritis in infants was *Rotavirus*. In the study by Sherif *et al.* 2015 [19] is shown that most of the breastfed infants with *Rotavirus* gastroenteritis had positive sIgA values in stool as opposed to those infants who were on milk formula. Those infants who were positive for sIgA in stool had a milder clinical picture and a lower frequency of vomiting. In our research, a statistically significant difference ( $p = 0.002669$ ) for the average number of vomiting 24 h before admission was registered between the first and second groups with less frequent vomiting in exclusively breastfed infants in the first group, where sIgA was positive in all stool samples. Regarding the number of liquid stools 24 h before admission to the hospital, a statistically significant difference was registered between the first and the second groups ( $p = 0.002152$ ). Sherif *et al.*, 2015 [19], did not prove statistical significance for the degree of dehydration between groups but in our study, the effect of sIgA on the degree of dehydration in infants showed a statistically significant association between the first and second groups for  $p = 0.004708$ . Similar results were obtained in the study of Fuchs *et al.*, 1996 [20], which found that infants who were not breastfed were at higher risk of dehydration than those who were exclusively breastfed ( $p = 0.006$ ). In our study, vomiting during the treatment was less common in infants in the first group versus the second group with a statistically significant difference between the average number of vomiting by  $p < 0.05$ . Regarding the average number of stools during the treatment, there was also

a statistical significance for  $p < 0.05$  between the first and second groups. In the study of Eaton-Evans and Dugdale, 1987 [21] has been shown that breastfed infants up to 6 months of age have a lower number of liquid stools and a lower vomiting frequency compared to those who were fed with other types of milk, indicating that breast milk has a protective effect on the intestines of infants younger than 6 months. In our study, we observed statistical significance for the number of days of parenteral rehydration between the first and second groups. For the number of hospital days, no statistical significance was proved either between the first and the second groups. In contrast to our results in a study by Boccolini *et al.* 2012 [22] was shown that the increase in the prevalence of exclusive breastfeeding in infants younger than 4 months with acute diarrhea has a negative correlation with the duration of hospitalization ( $Rho = -0.483$ ,  $p = 0.014$ ). Our study has shown that exclusive breastfeeding is effective in preventing *Rotavirus* infection by reducing the risk of *Rotavirus* infection in children, especially in the first 6 months of life, OR = 0.0758, 95% CI (0.0071–0.8074). This study had limitations because it was performed on a relatively small number of infants in a shorter follow-up period. During research of the published literature, we revealed a small number of studies examining the direct effect of breast milk sIgA on the severity of the clinical picture in infants with acute gastroenteritis. For getting more significant evidence-based conclusions, more studies such as this one, higher number of participants and follow-up over a longer period of time are necessary. This would emphasize the importance of breastfeeding, especially in the first 2 years of life, because breast milk provides high concentrations of sIgA that protects the intestinal epithelium of infants from damage in the presence of intestinal pathogens, as in this case protects, it from damage caused by *Rotavirus* acute gastroenteritis.

## Conclusion

In our study, we have shown that the presence of breast milk sIgA in infants has an effect on the severity of the clinical signs of acute gastroenteritis by reducing the vomiting frequency, the number and severity of diarrheal episodes, the risk for moderate and severe dehydration, and fever frequency.

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